University of Nevada, Reno

The strategy and motivational influences on the beneficial effect of neurostimulation: a tDCS and fNIRS study

A dissertation submitted in partial fulfillment of the
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By

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Abstract

The use and public knowledge of noninvasive neurostimulation is rapidly increasing. Transcranial direct current stimulation (tDCS) is a noninvasive technique in which small amounts of current are passed through the cortex in order to change the resting state of underlying neurons. This technique has wide use in rehabilitation and research settings. Here we studied the use of tDCS in healthy younger adults. Our previous findings demonstrated that tDCS can improve working memory (WM) performance in *some* individuals. We learned that individual differences in education level and WM capacity modulate tDCS effects. In Experiment 1 and 2 we investigated why low WM capacity participants do not benefit or have reduced performance after tDCS. We also explored how tDCS affects cortical blood flow using functional near infrared spectroscopy (fNIRS). In Experiment 1 we examined how strategy use influences tDCS effects. The results demonstrated that active strategy use does not facilitate tDCS effects in low WM capacity participants. Conversely, the high WM capacity participants continued to improve. Furthermore, we found that only the high WM capacity participants had an increase in oxygenated blood flow following anodal tDCS regardless of strategy use. In Experiment 2 we investigated how motivation level modified tDCS effects. We found that motivation level promoted enhanced performance across tDCS conditions for both WM capacity groups. Interestingly, only the low WM capacity participants had an increase in oxygenated blood flow across all motivation and tDCS conditions. The results from all four experiences have important implications for future successful use of neurostimulation in both clinical and healthy populations.

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Chapter I

General Introduction

In today's world our cognitive systems are constantly being pushed to the limits with the amount of information that we must retain and manipulate at any one time. While at work or home we are constantly juggling information in our head from a variety of technological mediums at once. We take our ability to multitask for granted and do not think twice about how cognitively taxing it is to text on a cell phone while paying attention to the game on television. The ability to hold and manipulate multiple items in our consciousness at once is called working memory (WM). This ability is crucial for our survival and ability to interact successfully in almost every daily task no matter how trivial. Given this importance of WM, maximizing the number of items that can be held at any one time is vital to successful cognitive functioning.

The following sections provide brief background information on the limits of WM and the neural mechanisms underlying WM. We further summarize attempts at extending the limits of WM through behavioral training paired with neurostimulation. Next we review studies that find empirical evidence for how individual differences in participants predict WM performance. Last we summarize our previous research in which we reported that individual differences predict the WM benefit seen following neurostimulation. These studies call in to question the use of neurostimulation in improving WM in the general population. These issues serve as the rationale for Experiments 1 and 2. In these experiments we address two factors, the use of cognitive strategy and participant motivation that may modulate neurostimulation effects on WM. Appropriate understanding of these factors will lead to the development of protocols that provide universal benefit from neurostimulation.

The Neural Correlates of Working Memory

Understanding what neural structures contribute to WM functions is vital to cognitive neuroscience research that attempts to improve WM. Patients with cortical lesions are important for researchers to determine the relationship between cognitive functions and areas of cortex. Furthermore, understanding where WM is taking place within the cortex allows for targeted enhancement of WM performance and capacity with neurostimulation techniques.

Frontoparietal networks interact to maintain and manipulate items in WM (Fuster, 1973; Goldman-Rakic, 1990, 1995). These networks include the prefrontal cortex (PFC) and the posterior parietal cortex (PPC; see Figure 1). The PFC has been classically identified as the region critical to actively manipulating items in WM (reviewed in (D'Esposito, Postle, & Rypma, 2000). More recent work has focused on extending cognitive models to identify the neural correlates of WM, including the contributions of the inferior and superior parietal lobes comprising PPC (for reviews see (Brady, Konkle, & Alvarez, 2011; Chein & Fiez, 2001; Cohen et al., 1997; Courtney, Ungerleider, Keil, & Haxby, 1997; Jonides et al., 1993; Linden et al., 2003; Munk et al., 2002; Olson & Berryhill, 2009; Pessoa, Gutierrez, Bandettini, & Ungerleider, 2002; Sala, Rama, & Courtney, 2003; Ungerleider, Courtney, & Haxby, 1998). These findings were an important basis for our previous studies (discussed below) using transcranial direct current stimulation (tDCS) to target PPC regions with the goal of providing convergent data for previously reported neuropsychological findings (Olson & Berryhill, 2009), and to modulate WM performance in healthy young adults (Berryhill, Wencil, Branch Coslett, & Olson, 2010; Jones & Berryhill, 2012).

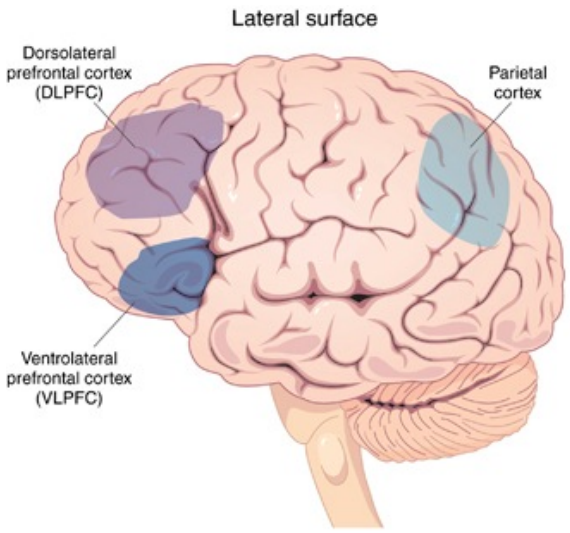

Figure 1: The PFC and PPC are highlighted to show the left lateral hemisphere of the cortex. These regions correspond to F3 and F7 respectively on the 10-20 EEG system. The purple and teal highlighted areas correspond with the regions of cortex described above (PFC and PPC respectively). The PFC has classically been associated with manipulation of items in WM as well as general executive functioning. The PPC has only more recently been associated with WM through fMRI research investigating capacity limits and patients with bilateral PPC lesions demonstrating impaired performance on WM tasks probed by recognition.

Given the relatively newfound observation of robust PPC activation in WM tasks the obvious prediction would be that damage to the PPC should cause some failures in WM tasks. This however turns out to be an oversimplification. Neuropsychological investigations in rare patients with bilateral PPC damage show selective impairment when WM is probed by recognition but not recall (Berryhill & Olson, 2008) when the retrieval demands were blocked, but not when they were unpredictable (Berryhill, Chein, & Olson, 2011). One possibility is that the PPC is relied on when participants adopt a passive, familiarity based strategy rather than a PFC-dominant active strategy, such as verbal rehearsal (Berryhill et al., 2011). We used these findings as a basis for our previous studies below. FMRI research reveals that strategy influences frontoparietal activity during visual recognition (Linke, Vicente-Grabovetsky, Mitchell, & Cusack, 2011). These findings account for differential activation patterns observed in the PPC when WM

is probed by recall versus recognition tasks (Chein & Fiez, 2001, 2010; Chein, Moore, & Conway, 2011). Specifically, during recognition WM trials greater PPC activity was observed, especially in tasks with a spatial component.

Models of Working Memory Capacity Limitations

Understanding what characterizes the limits of WM and how WM capacity can be extended is important for everyone interested in maintaining WM. Not only are these limits important to ecologically valid daily tasks, but understanding what our WM capacity limits are allows for more targeted attempts at improving WM. In this dissertation we review past attempts at expanding WM capacity. In the following experiments, we continue to use previous findings as a basis for conducting our studies with the long-term goal of improving WM capacity. Extending the limits of WM capacity is a goal that we have previously attempted through the use of neurostimulation (Berryhill & Jones, 2012; Jones & Berryhill, 2012), and is a goal we continue to pursue in this dissertation. Keeping a running subtotal as we shop, remembering a new acquaintance's name for a subsequent introduction, maintaining the distance of the car behind us as we switch lanes – these are further examples of daily activities that rely on WM. Learning how to improve WM capacity is an important area of research as capacity limits closely correspond with performance on important daily abilities such as reading comprehension (Daneman & Carpenter, 1980; Ehrlich, Brebion, & Tardieu, 1994; McVay & Kane, 2012; Meinz & Hambrick, 2010; Osaka & Osaka, 1994; Unsworth & McMillan, 2013a; Waters & Caplan, 1996), fluid intelligence (Kane et al., 2004), multitasking (Barrett, Tugade, & Engle, 2004), and problem solving (Conway, Kane, & Engle, 2003). Given the importance of WM, researchers have long attempted to classify the limits and function of WM.

Recent advances in cognitive neuroscience have moved the field forward from simple “box and arrow” models of WM capacity to actual evidence from the brain that makes theories testable. In the 1950’s George Miller presented his observation of WM capacity (G. A. Miller, 1956). Miller stated that we could mentally maintain about seven items at any given time (plus or minus two). This ‘magic number seven’ is now believed to be a gross overestimate of our actual WM capacity of around 4 items (reviewed in: (Cowan, 2001). Reaching seven items in WM is possible due to strategies such as chunking or grouping items together to make them easier to rehearse. Given the central role of WM in daily activities, cognitive researchers have devoted considerable efforts to developing and refining theoretical models of WM (for reviews see (Baddeley, 2000; Baddeley & Hitch, 1974; Chein & Fiez, 2010; Cowan, 1993; Cowan et al., 2005; Curtis & D'Esposito, 2003; Miyake, Friedman, Rettinger, Shah, & Hegarty, 2001; Oberauer, 2002).

Despite the large amount of research and theoretical models, questions still remain as to the exact nature of what items in WM actually represent in terms of storage unit. One question relates to the nature of WM capacity and how many items can be maintained at one time. One model of WM capacity, the discrete resources model, states that we can hold three to four items in WM at any given time with equivalent fidelity in a fixed number of ‘slots’ (Luck & Vogel, 1997; Pashler, 1988; Vogel, Woodman, & Luck, 2001). Contrary to this model, the flexible resources model states that we have a finite pool of resources that can be allocated in analog fashion across many items, but with additional items there is a cost in precision (Bays, Catalao, & Husain, 2009; Bays & Husain, 2008; van den Berg, Shin, Chou, George, & Ma, 2012; Wilken & Ma, 2004). The debate as to which model best represents how WM operates continues, and there are

many other models of WM resources, however a second debate relates to how *complex* these items in WM are is also ongoing.

The term complexity refers to the number of features comprising a stimulus. Some researchers find that the complexity of items in WM does not matter, that it is object-based, and a single item will fill one WM 'slot' regardless of complexity (Luck & Vogel, 1997). This is countered by studies that demonstrate a cost to WM as stimulus complexity increases (Alvarez & Cavanagh, 2004). These findings fueled the debate as to whether we hold features of items in WM or rather entire objects. Further evidence has shown that as precision demanded at recall increases, performance accuracy decreases (Zhang & Luck, 2008). If the discrete resources model is correct, participants' performance should remain constant as long as the number of presented items is fewer than that individual's WM capacity limit. This behavioral phenomenon was explained with a slots plus resources model (Zhang & Luck, 2008), which states that an item may be held in more than one slot at a time to increase the fidelity of its representation, and to subsequently improve recall accuracy. Therefore, when a single item occupies more than one 'slot', it reduces the total number of slots available to hold other information. These models of WM capacity and item complexity serve as relevant perspectives that clarify not only the range with which WM operates, but demonstrate the fact that any improvement in WM capacity will be significant to ecologically valid daily tasks.

Brain Activity Predicts Working Memory Capacity

Advances in cognitive neuroscience techniques have helped to shed light on WM debates using data from neural activity in the brain. Rather than only relying on behavioral measures of capacity in change detection tasks, researchers can investigate when and where the brain responds to items. Multiple methodologies are in agreement

as to the upper limit of WM capacity. Electroencephalography (EEG) studies show that after a stimulus is presented, brain activity reflects WM maintenance even though the stimulus is no longer visible. When items are presented to a single visual hemifield, representations are processed contralaterally in the brain. One way of looking at activity from the WM delay is to calculate the contralateral delay activity (CDA); contralateral – ipsilateral presenatations. These EEG studies show that CDA amplitude increases as set size increases (Vogel & Machizawa, 2004). Specifically, as a participant's WM capacity limit is approaches on a change detection WM task, the CDA also plateaus. Supporting this finding, evidence for an upper limit of WM capacity also comes from functional magnetic resonance imaging (fMRI) research. Similar to the CDA evidence above, activity in the PPC show that the BOLD response, similar to the CDA, increases with set size but asymptotes when set size expands past behavioral capacity estimates (Todd, Fougnie, & Marois, 2005; Todd & Marois, 2004). The BOLD signal is considerably slower as fMRI lacks the temporal resolution of ERPs. The EEG measurement of the CDA takes place over only one second and has high temporal resolution as compared to fMRI. Both techniques display the same pattern of data, however across very different time courses (CDA = millisecond temporal resolution, fMRI = second temporal resolution). Considering these fMRI data with CDA findings continue to provide evidence towards a discrete resource model of WM capacity as in both techniques the WM signal asymptotes at WM capacity.

As described above, there is a great deal of existing and ongoing research designed to answer questions regarding how many, and what kind of items can be held in WM simultaneously. This research can be applied towards the goal of maintaining or increasing the number of items that can be held in WM. However, these debates regarding WM capacity are likely of little interest to the general public even though the

implications of WM capacity are much more far reaching than they appear. If we know where in the brain, when it occurs, and how many items are maintained in WM, we can test ways to improve WM capacity limits. Understanding function-structure relationships is important to future (e.g. stem cell or neurostimulation) research that could enhance our cognitive capacity following brain injury or those that accompany the natural aging process.

How Can Working Memory Be Improved

Given the importance of WM, maintaining and expanding WM capacity is important to cognitive skills used in daily life. Understanding ways in which we can expand WM capacity will help to maintain and improve performance on ecologically valid tasks. Improving WM is not easy and often research studies report short-lived benefits or null results (L. L. Richmond, Morrison, Chein, & Olson, 2011). Understanding what factors will predict the greatest WM capacity gains is important not only in research settings, but vital to the increasing aging population.

Researchers have been attempting to maintain or enhance WM capacity (Bomyea & Amir, 2011; Chein & Morrison, 2010; Harrison et al., 2013; W. Zhang & S. J. Luck, 2011). Improving cognitive skills in general is applicable to a wide range of populations such as those with brain injury, older adults, and even enhancing memory in neurotypical adults. Multiple techniques have been developed for enhancing cognitive skills such as extensive training on cognitive tasks with the goal of widespread improvement. This has given rise to a large industry of brain training products (e.g. Lumosity, Brain Age), which sell the possibility of enhancing cognitive performance through repeated practice of computer-based tests. The goal of cognitive training is to improve performance on trained tasks that transfers to untrained tasks. However,

evidence of successful transfer of training benefit to untrained tasks is inconsistent (Dahlin, Nyberg, Backman, & Neely, 2008; Li et al., 2008; L. L. Richmond et al., 2011; Schmiedek, Lovden, & Lindenberger, 2010), and across WM training studies it is inconsistently assessed (Dahlin, Neely, Larsson, Backman, & Nyberg, 2008; Mahncke et al., 2006; Morrison & Chein, 2011). In other words, cognitive training alone is not enough to reliably ensure gains in WM capacity.

One goal of cognitive training with a broad public health component is to improve (Jaeggi, Buschkuehl, Jonides, & Perrig, 2008) or restore cognitive ability associated with age-related decline (Buschkuehl et al., 2008; Legault & Faubert, 2012; O'Brien et al., 2013; Park & Bischof, 2013; L. L. Richmond et al., 2011; Steinerman, 2010; van Muijden, Band, & Hommel, 2012). Because age-related decline in WM affects most individuals, and because WM function underlies complex cognition there is incentive to improve WM performance. WM capacity is difficult to expand in young adults; it is also challenging to maintain WM over the aging process. This decline as we age is likely caused by age-related cortical volume loss, particularly in frontoparietal regions engaged during WM tasks (Good et al., 2001; Raz et al., 1997). Furthermore, the possibility of enhancing the neurotypical brain to improve WM and attentional abilities is an exciting possibility. Cosmetic enhancement of the brain is a very real possibility through techniques such as transcranial direct current stimulation (tDCS). Not only is recovery from brain damage important, but so is enhancing WM capabilities and maintaining functioning across the lifespan. The possibility of extending our cognitive capabilities through enhancing our WM capacity has a wide range of benefits, as WM capabilities correlate with day-to-day tasks as well as fluid intelligence (Colom, Rubio, Shih, & Santacreu, 2006; Jaeggi et al., 2008; Unsworth, Fukuda, Awh, & Vogel, 2014). Given the

importance of WM and maximizing WM capacity, we attempt to expand WM performance through the use of tDCS in Experiments 1 and 2.

Transcranial Direct Current Stimulation In Cognitive Studies

As noted above, maintaining or enhancing cognition using neurostimulation may be possible. Over the last 10+ years researchers used neurostimulation techniques, such as tDCS, for understanding the relationship between regions of cortex and their functional contributions to WM (Andrews, Hoy, Enticott, Daskalakis, & Fitzgerald, 2011; Berryhill et al., 2010; Boehringer, Macher, Dukart, Villringer, & Pleger, 2013; Boggio et al., 2006; Dockery, Liebetanz, Birbaumer, Malinowska, & Wesierska, 2011; Ferrucci et al., 2008; Fregni et al., 2005; Heimrath, Sandmann, Becke, Muller, & Zaehle, 2012; Jeon & Han, 2012; Jones & Berryhill, 2012; Marshall, Molle, Siebner, & Born, 2005; Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011; Mylius et al., 2012; Ohn et al., 2008; L. Richmond, Wolk, Chein, & Olson, 2014; Zaehle, Sandmann, Thorne, Jancke, & Herrmann, 2011). Unlike the correlational method of fMRI, these data provide causal evidence of functional involvement in WM tasks.

To more clearly understand the contributions of neurostimulation in both clinical and cognitive studies, we review recent findings as well as proposed mechanisms responsible for behavioral changes. Transcranial direct current stimulation (tDCS) involves the application of small amounts of electric current to the scalp to modulate the excitability of underlying neural populations (Nitsche & Paulus, 2000, 2001). This technique is appealing because it is well tolerated, amenable to double-blind designs, safe, and affordable (Bikson, Datta, & Elwassif, 2009; Nitsche et al., 2003). During tDCS, current flow is determined by the placement of the anodal (+) and cathodal (-) electrodes. Anodal tDCS has been associated with the depolarization of neurons –

making them more likely to fire. Cathodal tDCS has been associated with hyperpolarizing neurons – making them less likely to fire (Nitsche & Paulus, 2000; Rosenkranz, Nitsche, Tergau, & Paulus, 2000). TDCS is thought to produce cognitive effects by modulating membrane potentials and the synaptic strength between stimulated neurons (Stagg & Nitsche, 2011b). This affordable and safe technique has the potential for future use in the general population. Animal research involving tDCS found that anodal tDCS increased neuronal activity and cathodal tDCS decreased neuronal activity, similar to the tDCS-induced patterns observed in the motor cortex of humans (Purpura & McMurtry, 1965). However, within deeper layers of cortex, the opposite effect was seen. Namely, anodal stimulation deactivated neurons and cathodal stimulation activated them. This suggested that neuronal orientation is an important factor when studying tDCS effects (Purpura & McMurtry, 1965). Within the cortex, tDCS modulates synaptic strength and likely stimulates neurons in the cortex, pyramidal neurons, and interneurons (Stagg & Nitsche, 2011a). Several neuromodulators such as GABA (Stagg et al., 2009), Na^+ and Ca^{2+} channel blockers (Nitsche et al., 2004), L-DOPA (Kuo et al., 2008), and D_2 receptor agonists (Monte-Silva et al., 2009; Nitsche et al., 2006) also have an effect on increasing and/or decreasing the effects of tDCS stimulation (for more see: (Stagg & Nitsche, 2011a). These previous findings implicate a wide range of possible factors that may influence how tDCS affects participants. The exact mechanism and relative importance of each factor is still unknown, and these factors likely modulate the effectiveness of tDCS between individuals.

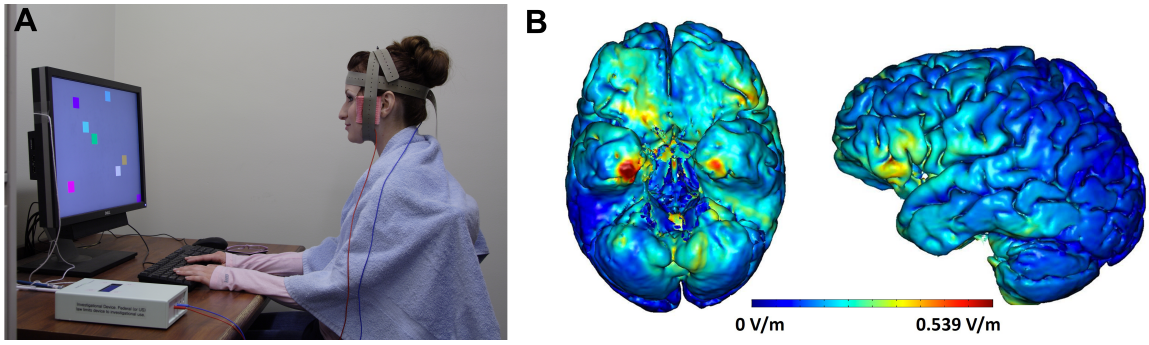

Figure 2: A) The standard tDCS set up while the participant receives stimulation. B) Current modeling of F3 anodal stimulation with the cathodal electrode on the right cheek. Models of current flow are important for predicting the path of least resistance between the two electrodes. Given the relative unknown of tDCS mechanisms, current modeling provides some clues as to which regions of cortex may be affected by tDCS as well as how diffuse the stimulation is underneath the electrodes. Red indicates areas affected by tDCS and current flow path. This analysis confirmed that tDCS to the PFC supplied current to PFC regions, but current also reached orbitofrontal and ventral temporal regions. High-resolution individualized models were derived from MRI data (1mm T2-weighted scan). The MRI scans were segmented into several tissues: skin, fat, bone, CSF, gray matter, white matter, air, and deep brain structures. Segmentation was carried out using Simpleware ScanIP (Simpleware Ltd., Exeter, UK). The electrodes were created in SolidWorks (Dassault Systèmes Corp., Waltham, MA) and oriented on the head using ScanCAD (Simpleware Ltd., Exeter, UK). The head, now with the electrodes placed, was imported back to ScanIP to generate a volumetric mesh and current flow was plotted on to the cortex (Bikson, Rahman, Datta, Fregni, & Merabet, 2012).

TDCS is an appealing research technique because it is safe, relatively affordable, and can modulate neural activity within the cortex. However, in the limited literature regarding tDCS and cognition, there are discrepancies that exist. The relationship between stimulation condition and its effects is not fully understood. One assumption of tDCS in studies of cognition is that anodal current creates an excitatory effect while cathodal current creates an inhibitory effect due to how the current flow affects the resting state of the neurons directly below the electrode (anodal = depolarize, cathodal = hyperpolarize). However, a recent meta-analysis indicated that this is commonly observed when the motor cortex was stimulated, but this pattern of tDCS related activation is less commonly seen in studies of cognition (Jacobson, Koslowsky, &

Lavidor, 2012). One explanation for this difference in the pattern of results is that cognitive abilities are more complex in nature than motor functions as participants are generally not moving but still have active WM during tDCS sessions. Motor behavior is not voluntarily activated during stimulation whereas WM is constantly being updated. This also may be because motor tasks are generally measured with motor evoked potentials whereas cognitive performance is measured in behavior performance measures, such as reaction time, accuracy, or through neuroimaging (e.g. fMRI, ERP, MEG). Motor evoked potentials are electrical signals recorded in muscles following tDCS to the motor cortex. These motor signals reflect the likelihood of muscle contraction whereas signals between regions of cortex interact with multiple excitatory and inhibitory signals.

Measures of cognitive task performance may also be more susceptible to external noise than measures of motor task performance. An example of this in cognitive studies using tDCS required stroke participants to name pictures, yet anodal and sham stimulation to left frontotemporal areas revealed no effect whereas cathodal stimulation significantly improved picture-naming accuracy (Monti et al., 2008). Another example is a study investigating the effect tDCS on risk-taking; non-marijuana users had an increase in conservative decision-making whereas the same stimulation had an increase in the propensity of risk-taking in marijuana users (Boggio et al., 2010). Our own research found that both anodal and cathodal tDCS had a beneficial effect on WM performance, but only in participants with high WM capacity (Jones & Berryhill, 2012). Lastly, reaction time on a visual Sternberg task slowed following bilateral stimulation of the lateral PFC (Marshall et al., 2005). There is also evidence that indicates cathodal tDCS may not be decreasing neural excitability, but, rather, it may be reducing competition between neurons (Antal et al., 2004). In summary, heuristics derived from

tDCS to motor regions do not translate to cognitive tasks and reflect the fact that the mechanism(s) of tDCS effects are not fully known.

TDCS has promise for enhancing learning and WM for the general public, however the mechanism is still not fully understood. Importantly, the knowledge of how to effectively improve cognitive functions is still being elucidated through research, but this has not stopped a large market of off-label do-it-yourself neurostimulation kits being sold to the general public (e.g. GoFlow, diytDCS.com). Understanding how to properly apply neurostimulation to healthy and clinical populations is critical as public knowledge of these techniques continue to grow.

Functional Near-infrared Spectroscopy as a Tool

Functional Near-Infrared Spectroscopy (fNIRS) is a noninvasive imaging technique that measures cortical hemoglobin oxygenation. In the current dissertation, we will employ fNIRS to measure activity within the cortex before and after the application of tDCS. This is important as most tDCS studies, including our previously published studies (Berryhill & Jones, 2012; Jones & Berryhill, 2012; Tanoue, Jones, Peterson, & Berryhill, 2012), rely solely on subtle behavioral differences without an understanding of how tDCS modulates cortical activity. Similar to measuring the BOLD response in fMRI, fNIRS measures cortical blood flow without the need of a large and costly magnet. Furthermore, fNIRS allows for measurements to be recorded in real time in laboratory settings. This technique is significantly cheaper than fMRI and importantly does not require the participant to be placed horizontally in a scanner during testing.

FNIRS measures the absorption of near-infrared light by the oxyhemoglobin (HBO) and deoxyhemoglobin (HBR) in the cerebral cortex (Chance, Zhuang, UnAh,

Alter, & Lipton, 1993; Edwards et al., 1993) based on differential absorption spectra. FNIRS, like fMRI, provides a proxy measure of neural activity by assessing changes in blood flow. The light signals are scattered across skin, skull, CSF and brain; but reflect back from oxy- and deoxy- hemoglobin. The photodetectors save the photons, which weren't emitted. Photon path follows a banana shaped path between the detector and light source (Figure 3). Hemodynamic changes for a given task occur in a time span of 6 to 8 seconds, and the sensors that collect the absorbed and non-absorbed fNIRS data measure the signal with a sampling rate 50 Hz. Oxygenation (HBO) corresponds to the difference between oxy-hemoglobin and deoxy-hemoglobin concentrations. A positive increasing difference between oxy- and deoxy-hemoglobin values suggest that there is an increasing demand for oxygen at that period of time, hence there is increased activation under the corresponding voxel (Izzetoglu et al., 2005).

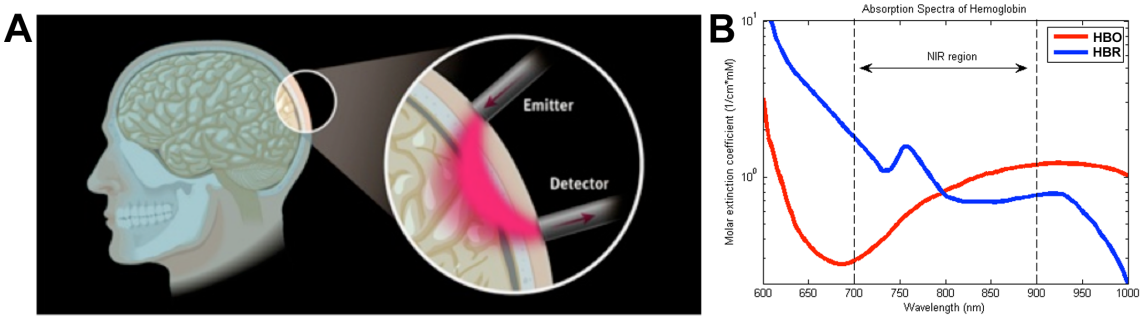

Figure 3: A) fNIRS system showing an emitter of infrared light, which passes through the cortex. This light bounces around in the cortex and returns to a detector, which reads the level of HBO and HBR blood at two different wavelengths. In the current Experiments we measure wavelengths 830 nm and 690 nm. When light enters the tissue, it scatters and interacts with the blood. The intensity of the light that exits the head and returns to the detector allows for a measurement of oxygenation level in the blood. Skin, tissue, and bone are transparent to the infrared light whereas HBO and HBR absorb the light. B) Multiple wavelengths are used in order to measure at two points in the absorption spectra. One point must be below the isosbestic point of 810 nm where HBO and HBR have the same absorption coefficient and one point must be above 810 nm.

FNIRS has been used to record cortical blood flow in cognitive and attention studies to elucidate specific contributions of regions of cortex by measuring the blood-oxygenated level dependent (BOLD) response (Cutini et al., 2008; Fallgatter & Strik, 1997; Herrmann, Ehlis, & Fallgatter, 2003; Honma, Soshi, Kim, & Kuriyama, 2010; Horovitz & Gore, 2004; Kubota et al., 2006; Leon-Carrion et al., 2006; Schroeter, Zysset, Kupka, Kruggel, & Yves von Cramon, 2002; Tian, Sharma, Kozel, & Liu, 2009). For example, fNIRS studies find that predictions of PFC activity during a deception task based on previous fMRI findings demonstrate a similar pattern (Tian et al., 2009). Furthermore, fNIRS can detect an increased hemodynamic response during incongruent trials in a Stroop task (Schroeter et al., 2002), during false recognition memory trials in an episodic memory task (Kubota et al., 2006), between genders in the response to emotional stimuli (Leon-Carrion et al., 2006), measure the switch cost in the PFC in a task-switching paradigm (Cutini et al., 2008), and verbal-fluency activations in the DLPFC during a verbal-fluency test (Herrmann et al., 2003).

Furthermore, although developmental research predominates, fNIRS has been used to study the hemodynamic response specifically in WM in both clinical populations such as ADHD (Ehlis, Bahne, Jacob, Herrmann, & Fallgatter, 2008) and schizophrenia (Lee, Folley, Gore, & Park, 2008), as well as neurotypical populations (Honma et al., 2010; Molteni, Butti, Bianchi, & Reni, 2008). One study found that DLPFC activation declines as a function of age in neurotypical individuals through the use of fNIRS (Kwee & Nakada, 2003). Complementing this finding, another study found that fNIRS recordings from the DLPFC found a linear relationship between BOLD response and cognitive load during n-back tasks (Fishburn, Norr, Medvedev, & Vaidya, 2014). These studies confirm that fNIRS can reliably detect WM based activity in the DLPFC.

Combining tDCS *and* fNIRS: Early Precedent

TDCS is rarely paired with other techniques due to the relatively new usage of the technique in cognitive neuroscience research. TDCS has a proven track record of successfully modulating behavioral performance (Jacobson et al., 2012), yet few researchers have paired tDCS with other methodologies to monitor neuronal activity. One of the innovations in this dissertation is that we pair tDCS with fNIRS in a novel paradigm to measure cortical activity before and after stimulation and WM training. Furthering our understanding of how tDCS modulates cortical activity is important to an expanding field of research. This knowledge will also further our understanding of what factors predict beneficial effects of tDCS on WM performance.

As previously mentioned, the majority of tDCS research relies on subtle behavioral changes in performance in both healthy and patient populations. While researchers report these behavioral changes, there is less progress in assessing how tDCS affects cortical activity. Only two previous studies have employed fNIRS to measure changes following tDCS. First, anodal tDCS to the PFC induced a significant increase in HBO from pre-tDCS levels which lasted up to 10 minutes after stimulation (Merzagora et al., 2010). Importantly, this study was between subjects in nature and the participants did not complete any WM task. The effect was specific to anodal tDCS; cathodal tDCS had a negligible effect on HBO levels.

In a second study, when fNIRS was combined with repeated arithmetic training, tDCS induced more a efficient neurovascular response during arithmetic calculation in the left DLPFC (Snowball et al., 2013). Five consecutive days of tDCS paired with the arithmetic training enhanced the speed of calculation and memory-recall based arithmetic learning. Furthermore, at a 6-month follow-up the participants who received anodal tDCS had long lasting behavioral and physiological modifications as compared to

sham. The length of this improvement is encouraging for both training and tDCS studies as tDCS may be the key to finding reliable transfer effects following cognitive training.

These findings provide support for the use of combining fNIRS with tDCS to gain insight regarding underlying neural changes. Pairing these methodologies has advantages in allowing for a hemodynamic measurement from within the cortex following tDCS. This type of measurement strengthens the implications of neurostimulation studies, as behavioral performance can be compared with cortical activity. Understanding how tDCS modulates cortical activity is important for the growing field of neurostimulation research. Furthermore, understanding the physiological changes that take place following tDCS can elucidate why certain individuals may not receive any benefit from neurostimulation.

Individual Differences in WM and the Effect of tDCS on WM

A vast literature describes individual and group differences in WM capacity (Aslan & Bauml, 2011; Barrett et al., 2004; Barreyro, Cevasco, Burin, & Molinari Marotto, 2012; Bleckley, Durso, Crutchfield, Engle, & Khanna, 2003; Broadway & Engle, 2011; Conway & Engle, 1996; Fenn & Hambrick, 2012; Lewandowsky, 2011; Luck & Vogel, 2013; A. E. Miller, Watson, & Strayer, 2012; Newman, Malaia, Seo, & Cheng, 2013; Sobel, Gerrie, Poole, & Kane, 2007; Unsworth, 2007; Unsworth & Engle, 2005, 2007). Along with WM capacity, WM strategy use differs across individuals with different WM capacities (Bailey, Dunlosky, & Kane, 2008; Baldwin & Reagan, 2009; Cokely, Kelley, & Gilchrist, 2006; Imbo & Vandierendonck, 2007; Unsworth & Spillers, 2010). Low WM capacity individuals are more distractible (Unsworth, 2007), rely on context for recall, and have fewer attentional resources (Conway & Engle, 1996; Kane, Bleckley, Conway, & Engle, 2001; Unsworth & Spillers, 2010). Recent research has shown that high WM

capacity participants adopted more efficent strategies in a category naming task compared to low WM capacity participants (Schelble, Therriault, & Miller, 2012). Importantly, however, when instructed to use the same strategy as the high WM capacity participants, the low WM capacity participants performed just as well. This suggests that it is not a fundamental inability but, rather, a lack of strategy implementation that can be remedied through explicit instruction. Low WM capacity individuals *can* employ successful strategies, but they may not do so spontaneously. Strategy training may be employed to enhance frontoparietal activity during WM tasks, particularly in low WM capacity individuals. In neurostimulation experiments, individual differences are not taken in to account for variance in the effects of tDCS (see below). Furthering our understanding of how individual differences modulate the effect of neurostimulation is critical given the growing use of the technique.

Strategy use is not the only factors that contribute to WM capacity and tDCS linked WM benefits. Other work has found that different genotypes, which reflect biological differences such as neurotransmitter level or ion channel subtypes, vary performance on cognitive tasks. As an example, the catechol-O-methyltransferase (COMT) gene codes for an enzyme that metabolizes catecholamines and it is particularly important for metabolizing prefrontal dopamine. A single point mutation in the COMT gene replaces one amino acid (val158met) and it is associated with differences in cognitive abilities (Aguilera et al., 2008; Bertolino et al., 2006; Bruder et al., 2005; Buckert, Kudielka, Reuter, & Fiebach, 2012; de Frias et al., 2004; Stokes, Rhodes, Grasby, & Mehta, 2011). Individuals with a greater number of Val alleles had slower reaction times on WM tasks as compared to the Met allele. There is also some evidence that COMT genotype has a significant effect on the volume of gray matter and parietal lobe activity, specifically in the Val/Val genotype. (Dumontheil et al., 2011).

Consequently, COMT genotype may play a role in determining how participants will respond to tDCS. This complex story will require collaboration between neuroscientists focusing on all levels to enable accurate prediction of the effect of tDCS. Understanding how genotype predicts WM benefits following tDCS requires significant further research. The combined effects from all the genotypes that influence ion channels, neurotransmitter levels, tDCS effects, and WM performance will take many years to fully understand. These current and future findings will be vital for providing guidance with which to maximize studies that attempt to expand WM capacity and tDCS linked WM benefits.

We previously found that individual differences predicted the amount and direction of benefit from tDCS. These studies demonstrated the importance that individual differences had in modulating the WM benefit seen following tDCS. These differences ended up either predicting a WM benefit or null and negative effects following tDCS and raised important questions that we seek to solve in this dissertation. First, we used anodal tDCS to target the left and right PFC in healthy older adults with the goal of improving WM performance (Berryhill & Jones, 2012). Twenty-five neurologically normal older adults received three counterbalanced sessions of tDCS (anodal left PFC (F3), anodal right PFC (F4), sham). Participants completed a challenging 2-back WM task with both a verbal and spatial trials. We predicted that anodal left PFC tDCS should improve performance on the verbal component of the 2-back due to the left hemispheres verbal contributions. We also predicted that right PFC tDCS should improve performance on the spatial 2-back. Interestingly, however, only those older adults with more years of education showed a benefit, and it was equivalent across stimulation condition, site and task. The older adults who completed fewer years of education had no benefit or showed impairment following active tDCS.

This finding demonstrated that tDCS to either PFC location improved performance on both 2-back tasks, however only in half of our participants. This finding adds to the growing research demonstrating that tDCS may not have uniform effects across tasks (Jacobson et al., 2012) and individuals. Understanding the mechanism that education level is related to that predicts tDCS linked WM benefits or decrements is vital to the increasing use of this technique in both research and rehabilitation settings.

In the second study, we tested PPC involvement in WM in healthy younger adults by applying tDCS to the right PPC during verbal and visual WM tasks (Jones & Berryhill, 2012). The goal of this study was to investigate the paradoxical findings from two separate studies where tDCS was applied to the right PPC. First, Berryhill found that cathodal stimulation to the right PPC lead to impaired performance on a WM recognition task while anodal and sham tDCS had no effect (Berryhill et al., 2010). This finding supported research in patients with bilateral PPC lesions, where recognition was impaired but recall was in tact (Olson & Berryhill, 2009), however in a healthy younger adult population. In a second study, Tseng found that right PPC anodal tDCS lead to improved WM performance on a change detection recognition WM task (Tseng et al., 2012). Importantly, there was no group differences in tDCS linked WM benefits based on WM capacity. These two studies targeted the same region of cortex, but the results were inconsistent.

We addressed this apparent incongruity by combining these two WM paradigms in a new group of neurotypical young participants with anodal, cathodal, and sham tDCS to the right PPC. We predicted that with a new group of participants, we would replicate only one of the findings. Finding a cathodal tDCS WM impairment in only the sequential presentation task and finding only an anodal tDCS WM benefit in the change detection task struck us as unlikely.

The results demonstrated that the easier sequential presentation task used in Berryhill 2010 had little to no impact in performance across any tDCS condition, however cathodal tDCS had a minor impairment on performance. The more difficult change detection task used by Tseng was impacted by anodal and cathodal tDCS. However, this depended on the participants' WM capacity. The high WM capacity participants had improved performance in both tDCS condition and the low WM capacity participants had an equal impairment in performance in both tDCS conditions. For difficult WM tasks, individual differences in WM capacity significantly impacts tDCS effects.

Next, in a second experiment we investigated how task difficulty plays a role in the effect of tDCS on WM and also investigated if the individual differences finding would be replicated in a new set of participants. We varied set size in the change detection task to be presented with 4, 6, or 8 items. We used the same tDCS protocol of anodal, cathodal, and sham right PPC stimulation. We found that as set size increased, so did the beneficial effect of anodal and cathodal tDCS, however again only in the high WM capacity participants. The low WM capacity participants had either no benefit or were impaired following tDCS.

This finding supports that of the previously discussed study in that only the high group (education, WM capacity) benefitted from tDCS. These results also reveal that task difficulty predict tDCS benefits, as the high WM capacity group showed a linear benefit as set size increased in the visual WM recognition task. While the findings from these two experiments support each other, there is not a clear rationale for why WM capacity and education level predict neurostimulation benefit. Both of these studies rely on subtle behavioral changes, rather than any measurement within the cortex.

Does WM Strategy and Motivation Predict tDCS Effects on WM?

There are a number of possible explanations for the group differences described above. Olson and Berryhill raised the hypothesis that patients with bilateral PPC damage are able to overcome WM deficits by employing an active rehearsal strategy that relies on the PFC for recall WM (Olson & Berryhill, 2009). Perhaps, those with low WM capacity or low education are not adequately engaging in WM strategy receive no WM benefit from tDCS. This gives way for a testable possibility that the high education and WM capacity group use more effective WM strategies and that this is what predicts benefit, not necessarily years of school attended. A difference in effective strategy use has previously been observed between high and low WM capacity individuals in reading comprehension (Budd, Whitney, & Turley, 1995) and reading span (Kaakinen & Hyona, 2007). In one study, participants who employed an active rehearsal strategy in the operation span test had increased performance as compared to other strategies (Turley-Ames & Whitfield, 2003). Extending these findings, the active verbal rehearsal strategy continued to be associated with higher Operation Span (OSpan) performance when compared with imagery and semantic strategy instructions. Low span participants particularly benefitted from the active rehearsal strategy the most. Furthermore, operation span performance has also been shown to predict strategy use and the ability to deal with interference during tasks (Cokely et al., 2006). Supporting these findings, high WM capacity participants are more likely to spontaneously use an effective strategy in memory tasks without explicit instruction (Schelble et al., 2012). Continued research is needed to elucidate why certain individuals receive negative or null effects from tDCS. Furthermore, these differential effects may be responsible for null findings in other neurostimulation studies.

One other explanation is differential motivation levels between high and low performing participants. In previous experiments, we often observe participants do not

express any desire to participate other than to receive course extra credit. This often leads to capacity scores of less than 1 item, well below WM capacity limits. Several studies have demonstrated that motivation can enhance performance on cognitive tasks (Brose, Schmiedek, Lovden, & Lindenberger, 2012; Krawczyk & D'Esposito, 2013; Roets, Van Hiel, & Kruglanski, 2013; Sanada, Ikeda, Kimura, & Hasegawa, 2013; Unsworth & McMillan, 2013), although Zhang and Luck found that financial motivations did not increase the quantity of items in WM at the expensive of quality (W. W. Zhang & S. J. Luck, 2011). Contrary to this, only one study has found that financial motivation can successfully improve WM capacity (Sanada et al., 2013). No previous study has investigated the role that motivation has on the beneficial effect of tDCS on WM performance.

Understanding how low and high WM capacity participants respond physiologically to tDCS, as well as strategy and motivation conditions is important in designing studies that will maximize the beneficial effects. With the rapidly growing use of recreational- and laboratory-based tDCS, it will be important to define what predicts the magnitude and direction of tDCS effects.

Current Studies: Specific Aims

This dissertation outlines a series of experiments aimed at furthering our understanding of noninvasive neurostimulation for targeted use in improving cognitive functions in healthy participants. Neurostimulation techniques, such as tDCS, can be successfully applied to improve functioning in a series of studies in clinical and neurotypical individuals. However, utilizing neurostimulation to *reliably* improve cognitive functioning such as WM remains yet to be resolved as current studies have inconsistent findings (Jacobson et al., 2012). These experiments will aim to address two specific

questions. First, for those who receive no WM benefit from tDCS, can we remediate this through strategy training to ensure beneficial effects across all individuals? Second, how do does motivation influence tDCS linked WM benefits in low WM capacity participants?

We conducted two experiments, which investigated two possible factors that might predict who garners a tDCS benefit. We hypothesized that strategy use may differ between high and low WM capacity participants due to previous findings, which find that high WM capacity participants spontaneously use more effective strategies (Cokely et al., 2006; Schelble et al., 2012; Turley-Ames & Whitfield, 2003). If proper strategy instruction can facilitate a tDCS WM benefit in individuals who previously did not benefit, then we will have found a way to circumvent previous null findings (Chapter II, Experiment 1). Another possibility is that the low WM capacity participants may simply lack the necessary motivation to perform well and, therefore, show no improvement following tDCS. If properly motivated, perhaps the low WM capacity participants will demonstrate the same degree of WM performance improvement as the high WM capacity participants (Chapter II, Experiment 2). If motivation modulates tDCS effects, we may have discovered a mediating factor that contributed to previous null or negative findings.

To develop paradigms that show maximal benefits, it is essential to determine if strategy or motivation can elicit greater tDCS-linked WM benefits. Understanding how factors, such as motivation and strategy use mediate tDCS effects are essential for designing effective tDCS studies. These factors will also contribute to a more complete understanding of the mechanism by which tDCS enhances cognition. This dissertation comprehensively investigates contributions of strategy, motivation, and other demographic factors to help identify the ideal tDCS candidate.

Chapter II

Investigating Causes for Differential Neurostimulation Benefit

Experiment 1: The Role of Strategy Use in the tDCS Benefit

Experiment 1 Introduction

TDCS has a proven track record of improving cognitive and motor functions in both neurotypical and patient populations (Hamilton, Chrysikou, & Coslett, 2011; Jacobson et al., 2012). This technique has the added bonus of being noninvasive, safe, and relatively affordable. The public knowledge of tDCS and the do-it-yourself use continues to rise with recent media attention to neurostimulation. Given the finding of no effect of tDCS or a negative benefit of tDCS in our previous studies (Berryhill & Jones, 2012b; Jones & Berryhill, 2012), understanding what factors are important for maximizing neurostimulation benefits are critical.

Individual differences, such as WM capacity, may be driving the differential effects of tDCS, which may be responsible for the previous null findings in half of our participants. Here, we investigate individual differences in strategy use and tDCS-linked WM benefits. In our previous Experiments, high WM participants benefitted from tDCS, perhaps because they employ active WM strategies. Low WM capacity participants received no benefit of tDCS, but behavioral work shows they can use active rehearsal strategies when cued. This difference in strategy use has been previously observed in studies investigating individual differences in WM capacity (Schelble et al., 2012). Alternatively, there may be other differences in neural resources or other factors that explain this difference. If effective or ineffective strategy use can account for group

differences, we predict that low WM participants will garner greater tDCS-linked WM benefits when they are cued to use an active rehearsal strategy. Understanding the factors that modulate the effect of neurostimulation is critical to translational tDCS application.

If the magnitude of the tDCS-linked WM benefit is due to strategy use, then we should observe an interaction with strategy use and WM capacity where low WM capacity participants show a tDCS benefit when given an active strategy and the high WM capacity group should be impaired by a passive strategy (figure 4, top). If strategy use does not predict tDCS benefits, then we should replicate previous findings where high WM capacity participants show a tDCS benefit regardless of condition and low WM capacity participants have no benefit (figure 4, bottom). If low WM capacity participants continue to show no benefit from tDCS when given an active strategy, then other factors such as motivation (Experiment 2) or differences in available neural resources might be more important in modulating the effect of tDCS.

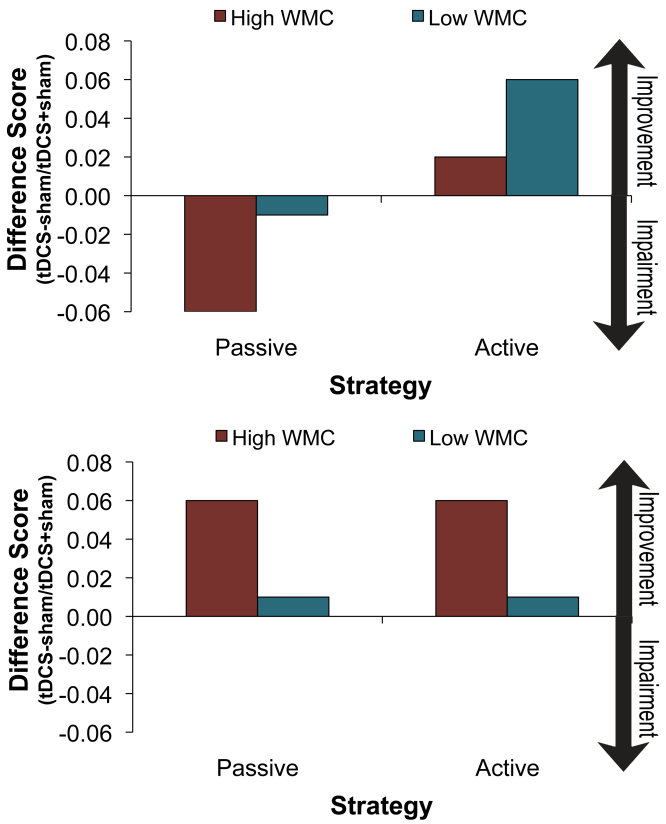

Figure 4: Predicted Exp. 1 results. Bars represent difference scores from sham. Top) If the hypothesis of strategy use predicting tDCS benefits is correct, then providing an active strategy to low WM capacity group should lead to large performance gains and a passive strategy to the high WM capacity group will impair performance. Bottom) If strategy use is not important for predicting tDCS benefits, then the high WM capacity group will benefit from tDCS regardless of strategy and the low WM capacity group will show no benefit.

Previous tDCS studies of cognition rely solely on subtle changes in behavioral performance without an understanding of changes within the cortex. Here we will investigate group (WM capacity) differences in neurovascular patterns during WM. To do this, we will employ fNIRS to detect changes at the left PFC between different strategy and tDCS conditions between the different participant groups (low or high WM capacity). If strategy use differs between participants with different WM capacities, then we should see distinctly different patterns of activation for the low and high WM capacity groups

during baseline. When provided with an active strategy, the performance of low WM capacity participants should improve. This improvement should also reflect HBO level changes in the PFC. We targeted the PFC due to previous fNIRS and tDCS research showing successful application of both techniques to modulate and measure performance. Furthermore, the left DLPFC will reflect active maintenance and verbal rehearsal during active strategy conditions. Supporting this is the improved performance in the previously mentioned bilateral PPC patients when forced to conduct an active verbal rehearsal strategy, thus effectively avoiding any reliance on the damaged regions of cortex (Olson & Berryhill, 2009). Furthering the understanding of how tDCS affects changes within the cortex is critical to future active use of neurostimulation.

If active strategies lead to greater PFC activity, then there should be a greater level of HBO in the PFC during active strategy blocks (Figure 5, top). The low WM capacity group should show a large increase in PFC HBO levels during active strategy blocks as compared to the preliminary task. During passive strategy use, we should see lower HBO levels in the PFC. We predict that tDCS will further enhance blood flow at the point of stimulation and interact with strategy use where PFC stimulation combined with an active strategy should show the greatest level of HBO. If strategy is not a driving factor in the effect of tDCS, then we should see no HBO level change from the preliminary task, regardless of strategy for the low WM capacity participants, whereas the high WM capacity participants will replicate previous findings and improve in all tDCS conditions (Figure 5, bottom). Combining tDCS and fNIRS will also allow for comparison between sham and active stimulations. The change in blood flow following tDCS will likely vary between participants with a low and high WM capacity based on our Experiment 2 findings. Given the relative unknown mechanism of tDCS, such as the

specific neurovascular changes following stimulation, further understanding of changes within the cortex is critical.

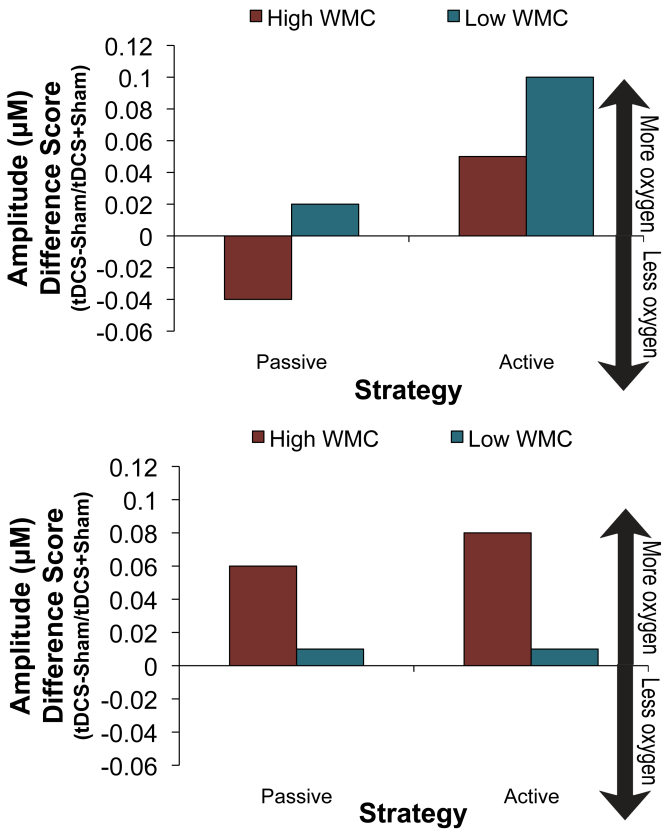

Figure 5: Predicted fNIRS data. Bars represent HBO levels at the left PFC. Top) If the predicted hypothesis of increased PFC HBO levels during active strategy use in the low WM capacity participants is correct, we should see a large increase for the low WM capacity participants in this condition. Anodal stimulation should also increase HBO levels in the high WM capacity group. Bottom) If strategy use does not modulate PFC HBO levels, we will see no change between passive and active strategy for either WM capacity group.

Experiment 1 Methods

20 neurotypical right-handed University of Nevada students (mean age: 24.20, standard deviation (SD): 3.81, 8 females) participated. Participants were screened for use of neuroleptic, hypnotic, or seizure medications. Participants reported no history of neurological or psychiatric symptoms or head injuries. All procedures were conducted in

accordance with the University of Nevada Institutional Review Board. Participants were compensated $15/hour and signed informed consent documents for both tDCS and fNIRS. Preliminary data suggest that high and low WM groups apply different strategies, but this may not be true in a new sample of participants. If not, we will investigate what strategies participants employ when given no instructions (baseline) and how strictly participants adhere to the strategy instructions.

Transcranial Direct Current Stimulation

There were two counterbalanced sessions: anodal tDCS (active) and sham (control condition). In both conditions, one electrode was placed over the left DLPFC directly between F3 and F7 (International 10-20 EEG system) and the reference electrode was placed on the contralateral cheek. This reference site is commonly used in a neurostimulation studies (Berryhill & Jones, 2012a; Berryhill et al., 2010; Elmer, Burkard, Renz, Meyer, & Jancke, 2009; Hsu et al., 2011; Jones & Berryhill, 2012; Marshall et al., 2005; Tanoue et al., 2012; Tseng et al., 2012; Zaehle et al., 2011). After 10 minutes of stimulation, the electrodes were removed and the fNIRS setup began. The effects of tDCS last are thought to last approximately one hour (Nitsche, Liebetanz, et al., 2003; Nitsche, Nitsche, et al., 2003; Nitsche & Paulus, 2000, 2001; Ohn et al., 2008). All tDCS sessions included a washout period of at least 24 hours.

Functional Near-Infrared Spectroscopy

All neurovascular recordings used a continuous wave fNIRS system (TechEn CW6 fNIRS System, Milford, MA). There was a single emitting source surrounded by three detectors spaced 2.6 cm apart. The detectors and source were attached to a fixed headband so that the distance remained constant between all participants (figure 6 B). In

order to ensure exact placement of the source and detectors between sessions, a photograph was taken of the head with the areas marked on the scalp. During set up of the fNIRS, all channels were required to meet our predetermined threshold of respiratory pattern at the 690 wavelength. If the pattern of blood flow was noisy the fNIRS set up was adjusted until the pattern was clear. Set up time for all participants took ~5 minutes to ensure that tDCS effects did not significantly dissipate.

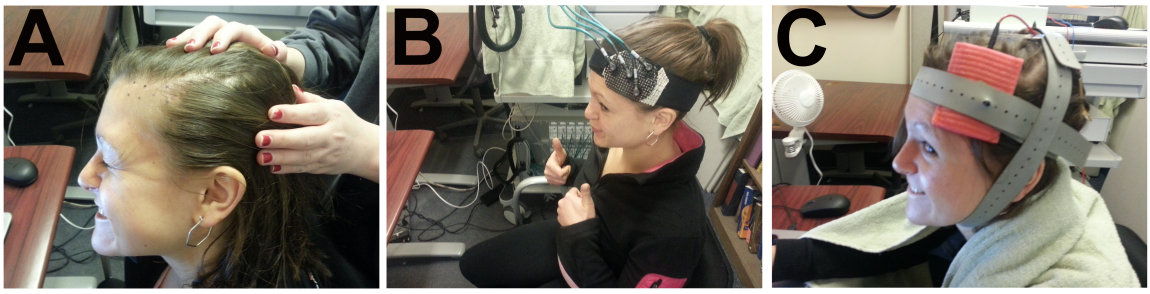

Figure 6: Example fNIRS set up. A) The participant has their head marked to correspond with where the emitter and detectors will be located. Next the participants' hair is parted to ensure the fNIRS is making contact with skin and not hair. B) The fNIRS is strapped to the participant and the signal is checked at 830 and 690 wavelength to ensure a good signal. C) fNIRS strap is removed and the participant receives 10 minutes of tDCS to the same location that fNIRS is targeting.

Behavioral Tasks

The Automated Operation Span (OSpan)

At the beginning of each session, participants initially completed the OSpan prior to application of the fNIRS and tDCS. This is a task of divided attention in which participants must solve true/false arithmetic problems while simultaneously encoding and maintaining a list of letters in correct order (Unsworth, Heitz, Schrock, & Engle, 2005) . Participants recall the letters after completing the arithmetic problems. The task lasted ~5 minutes and consisted of 4 sets of letters, which ranged from 4 to 7 total

letters. We measured performance by letter recall and math accuracy (scores range from 0 to 22).

Working Memory Strategy Task

After the OSpan, and the fNIRS montage was in place, the participant completed a preliminary WM strategy task. The task begins with participants being presented with four items (1000 ms) followed by a (5000 ms) delay period. The items were geometric shapes that were not easily named. Following the delay period participants were presented with only one item and were required to make an old/new recognition choice within 2000 ms. After every three trials there was a 15 second wait period to allow for the BOLD response to return to baseline. Participants completed 8 blocks of 3 trials, lasting ~6 minutes. At the end of the preliminary task participants were asked to describe the strategy they employed to complete the task as well as a judgment of their motivation. Following completion of the preliminary task, fNIRS was removed from the participants' head and 10 minutes of tDCS was applied to the same location.

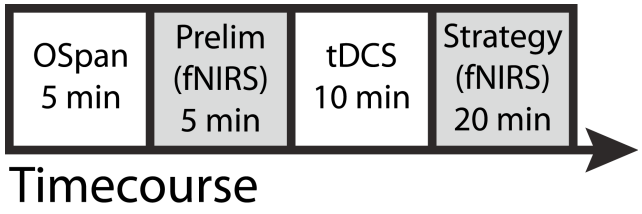

Figure 7: The order of the tasks in Experiment 1 (and 2). First the participant conducts the Operation Span task, which lasts roughly five minutes. Next, the participant has their head marked for the location of the emitter and detectors (see Figure 6 A) and the fNIRS system is placed on the head. Once a good signal is obtained, the participant conducts the preliminary WM recognition task. Following this task, the participant is set up with tDCS and receives 10 minutes of stimulation. Following stimulation, the tDCS is removed and the fNIRS is reapplied to the same location. After a good signal is obtained, the participant completes the final WM task.

Following tDCS, fNIRS was reapplied to the scalp in the same location as marked by permanent marker on the scalp. Participants then completed the preliminary task again, however during this task they were given explicit strategy instructions. Prior to the first block of 3 trials, participants were instructed to employ an active, verbal rehearsal strategy that required naming and rehearsal of the geometric shapes during the delay period. The following block of 3 trials had participants passively view the items, but instructed the participant to refrain from any rehearsal or internal verbal thoughts. Participants completed 15 blocks balanced of each strategy instruction. There were two versions of the strategy task with different sets of geometric stimuli to avoid naming of the items and the preliminary task also had unique geometric shapes. These versions were counterbalanced for order across participants. All other aspects of the strategy task were consistent between sessions.

Experiment 1 Analysis

For each participant, we calculated normalized difference scores for each session (anodal, sham) and strategy (active, passive) as follows: [(session accuracy – preliminary accuracy)/(session accuracy + preliminary accuracy)]. High and low WM capacity groups were determined by a medium split on the performance on the OSpan (high mean 19.90 (1.52), low mean 13.4 (3.50), $p < .001$).

Each block of trials lasted exactly 25 seconds followed by a 15 second rest period. The fNIRS data was parsed to collect an average HBO level for the final 20 seconds of each block for each of the three channels. The analysis focused on the mean oxygenation value (HBO) for each block, as we wanted to investigate how the BOLD response in the left DLPFC changed between conditions. Concentration changes of oxygenation are obtained from a modified Beer–Lambert approach (Chance et al.,

1998). Low pass filter with cut-off frequency of 0.5Hz was applied to the raw fNIRS data to eliminate high frequency noise due to physiologically irrelevant data (such as respiration, cardiac cycle and heart pulsation effects) and equipment noise. As above, we calculated normalized difference scores, but for each of the 3 detector channels, session (anodal, sham), and strategy (active, passive) as follows: [(session HBO level – preliminary HBO level)/(session HBO level + preliminary HBO level)].

Experiment 1 Results

Behavioral Effects

In Experiment 1, we were interested in understanding how strategy might play a role in the difference in performance between participants with different WM capacities. To answer this question, we conducted a two session (anodal, sham) x two strategy condition (active, passive) repeated-measures ANOVA with the between group factor of WM capacity (high, low) for the normalized difference scores. There was a no significant main effect of tDCS session ($F_{1, 18} = 1.69$, $p = .21$, partial $\eta^2 = .09$). However, there was a main effect of strategy condition ($F_{1, 18} = 13.00$, $p < .01$, partial $\eta^2 = .42$) such that an active strategy improved performance more than the passive strategy. The three-way interaction between tDCS condition x strategy x WM capacity reached significance ($F_{1, 18} = 10.61$, $p < .01$, partial $\eta^2 = .37$). The high WM capacity participants benefited more from anodal tDCS than the low WM capacity group and the high WM capacity group also benefitted the most when using the active rehearsal strategy (Figure 8, 9). These two factors when taken together (anodal tDCS + active strategy) lead to the greatest improvement for the high WM capacity group, while the low WM capacity group failed to show benefit. All other interactions failed to reach significance (all p's > .19). Participants

reported no differences in how closely they adhered to the strategy instructions or in motivation level.

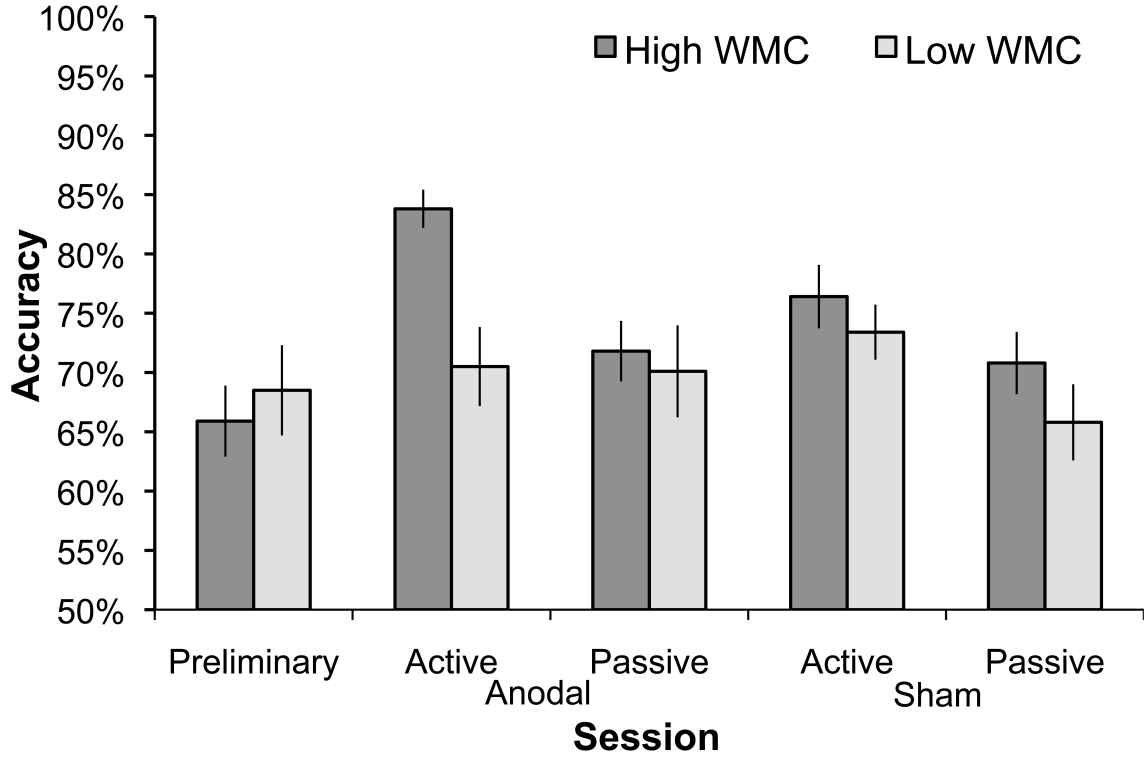

Figure 8: Behavioral results (raw accuracy) for Experiment 1. The dark gray bars represent the high WM capacity group and the light bars represent the low WM capacity group. Groups performed equally during the preliminary task. The high WM capacity group had a greater WM benefit following anodal tDCS. This difference was most apparent during the active rehearsal and anodal tDCS session.

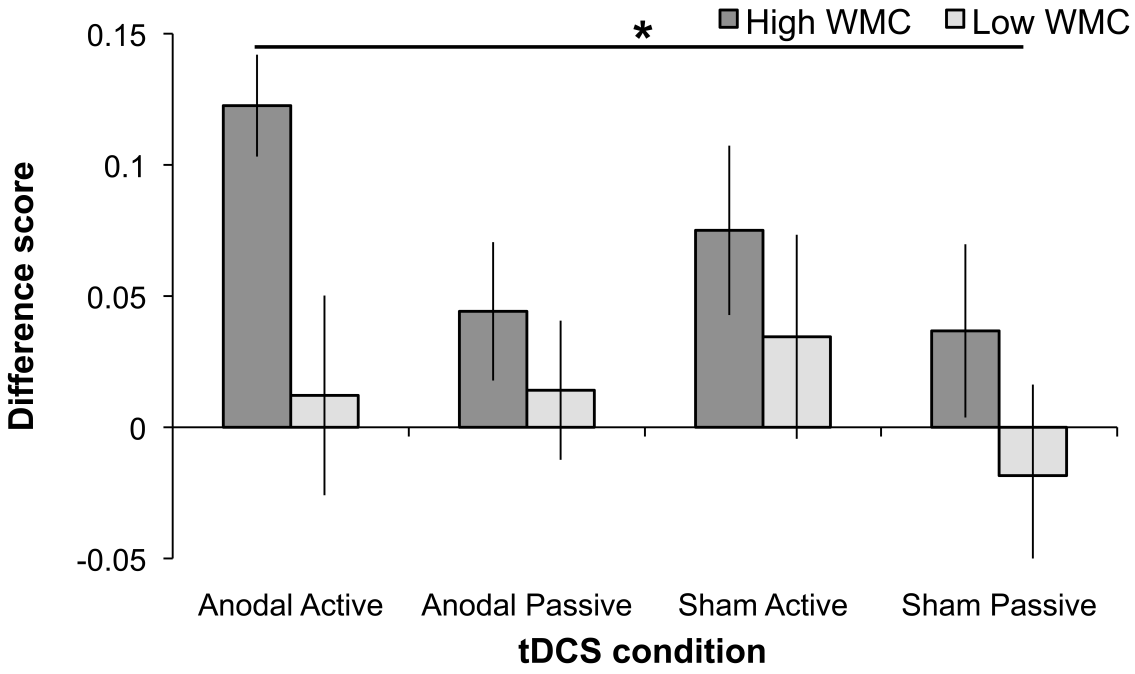

Figure 9: Bars represent the accuracy difference score from preliminary task for each condition. The active strategy did not help the low WM capacity participants as predicted. Anodal tDCS helped the high WM capacity group and did not help the low WM capacity participants regardless of strategy condition.

Functional Near-Infrared Spectroscopy Results

One low WM capacity participant was excluded due to excessive motion artifact in the fNIRS data. We were interested in how tDCS would alter the left DLPFC BOLD signal as measured by fNIRS. Furthermore, we were interested in understanding group differences in the fNIRS difference scores between tDCS and strategy conditions. To answer these questions, we conducted a two session (anodal, sham) x two strategy condition (active, passive) x three detector channel repeated-measures ANOVA with the between group factor of WM capacity for the normalized difference scores. There was a borderline significant main effect of tDCS ($F_{1, 17} = 3.61$, $p = .07$, partial $\eta^2 = .18$) and fNIRS channel ($F_{2, 34} = 2.95$, $p = .06$, partial $\eta^2 = .15$). There was no main effect of strategy condition ($F_{1, 17} = 1.80$, $p = .19$, partial $\eta^2 = .10$). The interaction of tDCS

condition and strategy neared significance ($F_{1, 17} = 2.48$, p = .09, partial η^2 = .16), as did the interaction of tDCS and fNIRS channel ($F_{2, 34} = 3.05$, p = .06, partial η^2 = .15). However, the interaction of strategy and fNIRS channel was significant ($F_{2, 34} = 3.11$, p = .05, partial η^2 = .15) such that the active strategy increased HBO levels at the left DLPFC. Finally, the interaction of tDCS, strategy, and fNIRS channel was significant ($F_{2, 34} = 3.49$, p = .04, partial η^2 = .17). No other interactions reached significance (all p's > .36), such that the high WM capacity group had a greater increase in HBO levels across active strategy and anodal tDCS conditions.

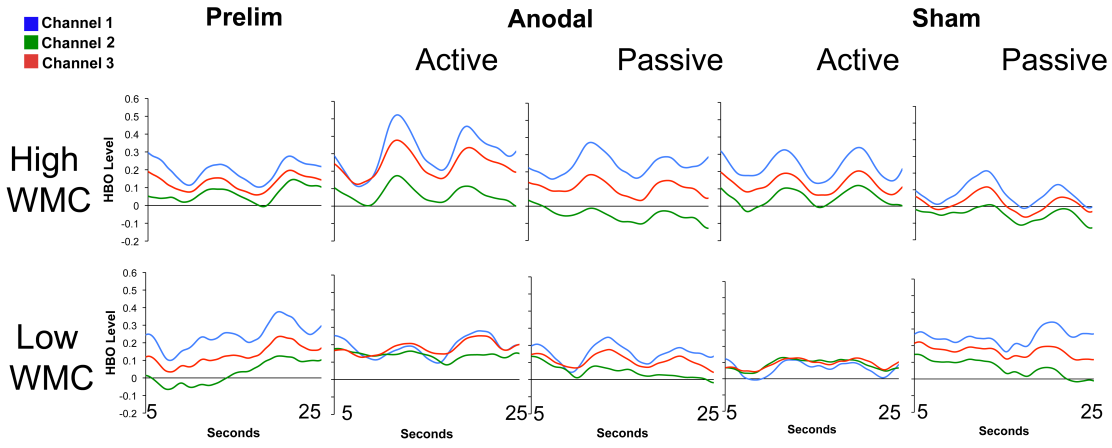

Figure 10: fNIRS data plotted as the HBO level through the block. The colors represent the three different channels. Graphs are plotted for the high WM capacity group (top row) and the low WM capacity group (bottom row). Plots represent data from the final 20 seconds of the trial averaged across all trials for that tDCS and strategy condition.

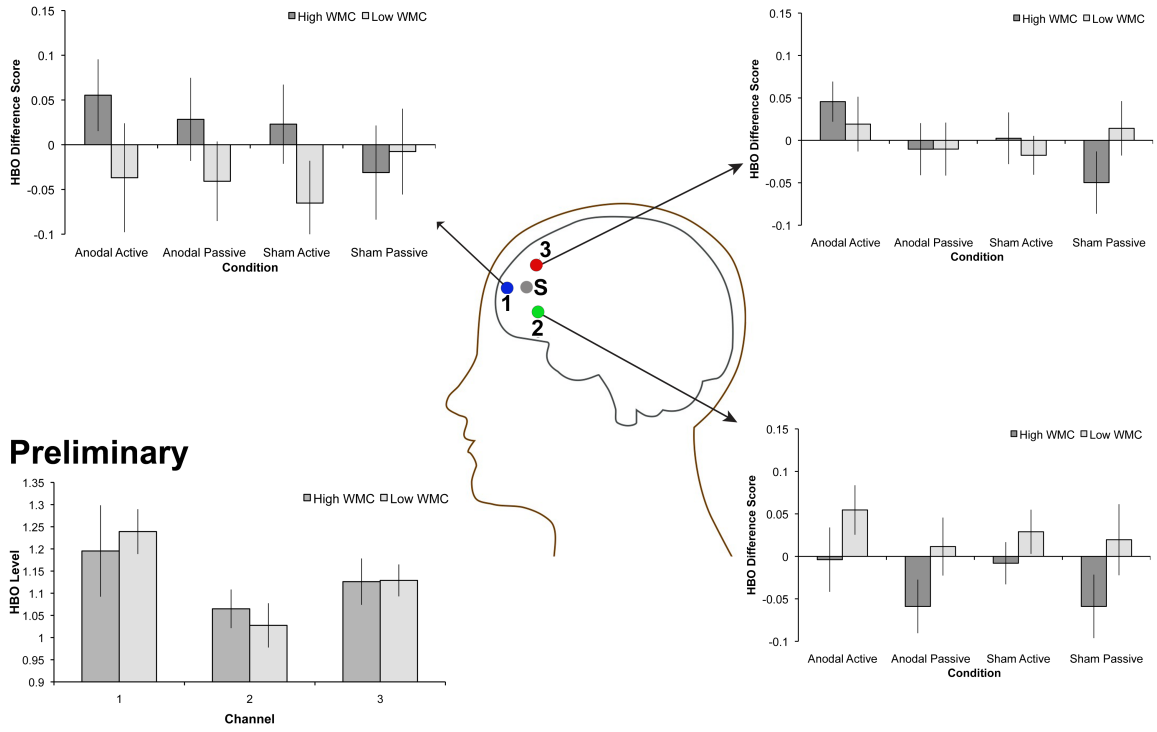

Figure 11: The difference scores for HBO levels between the preliminary task and each of the tDCS and strategy conditions for the high and low WM capacity groups at channel 1, 2, and 3. At channel 1, the high WM capacity group had an increase in HBO levels as compared to the preliminary task during both active conditions as predicted. However the HBO increase for the high WM group during the anodal passive condition and not sham passive condition can only be a result of stimulation. The low WM capacity participants had no change or a decrease in HBO levels in all conditions in channels 1 and 3. Bottom Left) The raw HBO levels during the preliminary task. Both the high and low WM capacity group had similar levels of oxygenated blood during the preliminary task prior to both tDCS and strategy instructions.

Experiment 1 Discussion

In Experiment 1, we were interested in the effect of an explicit verbal rehearsal strategy on WM performance, particularly for the low WM capacity group. The first question was whether the active strategy would improve performance of the low WM capacity group to match that of the high WM capacity group. Furthermore, we predicted that providing an active strategy to the low WM capacity group would enhance the benefit of anodal tDCS to the left DLPFC. This was not the case: the low WM capacity participants showed no benefit of tDCS. The high WM capacity group improved

during/following both active strategy conditions but showed the greatest increase following anodal stimulation (Figure 11). These behavioral results demonstrated similar patterns as seen in Experiment 1 and Experiment 2 where the high WMC group (education level and WM capacity) benefitted from tDCS and the low group showed no benefit. Interestingly, the low WM capacity group showed no benefit of an active strategy and had similar results across all tDCS and strategy conditions. Consequently, we must reject the hypothesis that poor strategy use explained the lack of a tDCS benefit in the low WM capacity group.

Neurally, the data demonstrate that the low WM capacity group had no change in HBO levels from the preliminary task across all tDCS and strategy conditions (figure 11). This was contrary to our prediction and taken with the behavioral findings provides strong evidence that effective strategy use is not enough to boost performance and HBO levels in low WM capacity participants. We observed an interesting pattern when comparing the high WM capacity difference scores; see figures 9 and 11. The behavioral benefit seen in the high WM group closely mirrors the BOLD response at channel 1. The increase in the HBO levels during the anodal passive condition, in the high WM capacity participants, suggests that strategy is not what is driving the differences in the BOLD response but rather innate differences between participants' response to neurostimulation. This is interesting because the difference in the BOLD response during the anodal passive condition cannot be explained by strategy as both groups reported adhering to the passive strategy. As participants had no incentive to lie, either they responded different physiologically or the high WM capacity group had difficulty preventing verbal rehearsal. This can only be explained by other factors, such as motivation level or biological differences between participants. Channel 2, the more inferior of the 3 fNIRS detector sites, did follow the predicted pattern of decreased HBO

levels in the passive strategy condition for the high WM capacity participants. This may reflect a reduction in HBO as compared to the preliminary task due to the use of a passive recognition strategy, a change we do not observe in the low WM capacity participants.

The results of Experiment 1 answer the question put forth in the specific aims. We predicted that effective strategy use would allow for equivalent performance between low and high WM capacity participants and tDCS benefits both groups. However, this turned out not to be the case. The low WM capacity participants continued to receive no benefit from tDCS, regardless of strategy condition. Interestingly, the high WM capacity group showed a benefit from tDCS during both active and passive strategy conditions suggesting that other factors must be playing a role and that these factors in some way influence WM capacity. It is critical to elucidate how tDCS can be successfully applied to everyone, especially those who are in the greatest need of cognitive improvements. Experiment 2 investigates the other prediction for causes that could be driving the variable effect of tDCS between participants.

Experiment 2: Motivational Factors in the Beneficial Effect of tDCS

Experiment 2 Introduction

One orthogonal possibility explaining individual differences in tDCS effects is that low WM capacity participants are simply low motivation participants. While motivational factors modulate WM performance, a previous behavioral study failed to find a significant improvement in visual WM capacity regardless of financial incentives (W. Zhang & S. J. Luck, 2011). However, ERP research has observed that high motivation (monetary) WM trials significantly improved behavioral performance and modulated late-trial processes (CDA, P300, (Sanada et al., 2013). FMRI studies demonstrate that the

ventromedial PFC encodes the current motivational significance (reward value, (Kringelbach & Rolls, 2004). Furthermore, financial motivation can modulate WM performance via amplification of activity within prefrontal and visual association regions (Krawczyk & D'Esposito, 2013a). Other fMRI research implicates other PFC regions, the right lateral orbitofrontal (OFC) and left dorsolateral PFC (DLPFC), respond differentially based on motivational condition (Szatkowska, Bogorodzki, Wolak, Marchewka, & Szeszkowski, 2008). Specifically, in the high-motivation condition, the right lateral OFC exerts an inhibitory effect on the left DLPFC. This is interpreted as the normal response to increased stress. Given these known contributing areas to motivation during WM, tDCS benefits may be influenced based on differential activation patterns under high and low motivation conditions.

Understanding the factors that modulate the effect of neurostimulation is critical to successfully applying tDCS. Furthermore, WM capacity differences may correlate with intrinsic motivation level. Low WM capacity participants may only require proper motivation to demonstrate superior WM performance and tDCS gains. If some participants lack motivation, or if memory tasks lower morale, tDCS-linked WM performance may be artificially low. This question of motivation must be clarified as new approaches to WM improvement emerge. Left PFC activity is believed to modulate WM performance based on motivation. If low levels of intrinsic motivation are responsible for low WM capacity participants not benefitting from tDCS, then providing high levels of motivation should benefit low WM capacity participants the most. If this hypothesis is correct, we should see a large increase in low WM capacity participants performance during high motivation conditions (Fig 18, top). If motivation is not a driving factor in the effect of tDCS, then we should see no improvement from sham regardless of incentive level for the low WM capacity participants whereas the high WM capacity participants

will replicate previous findings and improve in all tDCS conditions (fig 18, bottom). If different level of motivation can modulate WM gains from tDCS, then future studies can be designed to maximize performance. Proper motivation may be the key to improving performance in low WM capacity participants in tDCS studies.

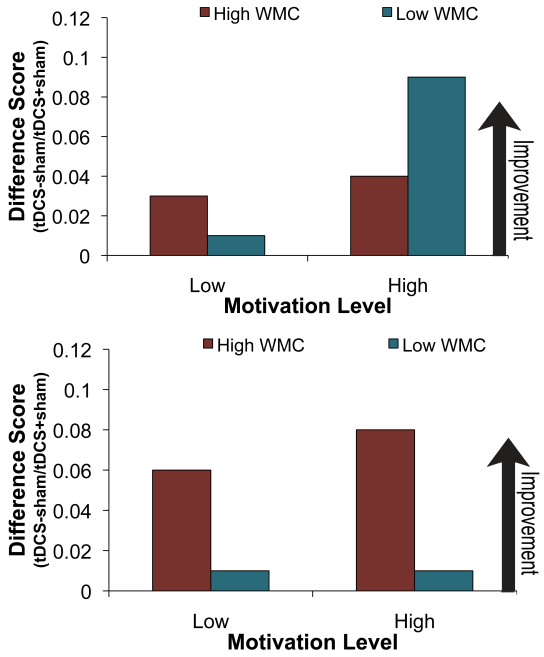

Figure 12: Bars represent difference scores from sham. Top) If the hypothesis that high motivation leads to increased tDCS benefits then the low WM capacity participants will be selectively helped by tDCS in the high motivation conditions. Bottom) If the hypothesis is incorrect, then the high WM capacity participants will replicate preliminary findings where tDCS will be beneficial regardless of motivation.

As with Experiment 1, here we will investigate how motivation modulates neurovascular patterns during WM tasks. The PFC has been shown to correlate with motivation level (Szatkowska et al., 2008). By measuring neurovascular activity in the left PFC during low and high motivation conditions, as well as pre- and post-tDCS we will be able to further understand how tDCS interacts with motivation and WM capacity. The same paradigm and stimulation parameters from Experiment 1 will be used. This will

allow for comparison of activation differences between participants with different WM capacities as well examining activity differences in motivation level. Understanding how motivation and neurostimulation modulate cortical areas associated with motivation level and WM are critical to successful application of tDCS across populations with varying WM capacities.

We predict that high motivation conditions should lead to greater PFC activity, as measured by a greater level of HBO levels. During low motivation conditions, we should see a smaller HBO level in the PFC. If our hypothesis of low motivation being responsible for previous null tDCS findings in low WM capacity participants, we should observe a large increase in HBO levels during high motivation conditions (Fig 19, top). If this hypothesis is incorrect, we will observe only the high WM capacity participants having increased HBO levels regardless of motivation condition, replicating previous findings (Fig 19, bottom). Combining tDCS and fNIRS will also allow for a comparison of activity changes between sham and active stimulations. The change in blood flow following tDCS will likely vary between participants with a low and high WM capacity based on our Experiment 1 findings.

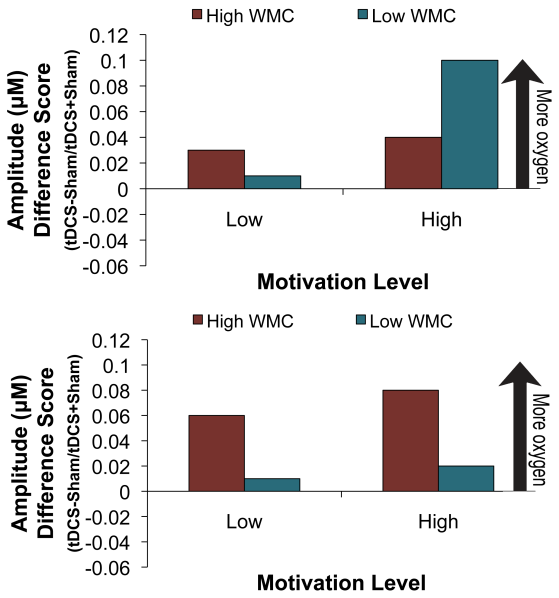

Figure 13: Bars represent HBO levels at the left PFC. Top) If the hypothesis of low motivation in the low WM capacity group is responsible for preventing beneficial tDCS effects, then the HBO levels should reflect this prediction. Low WM capacity participants should have a large increase in the high motivation condition. Bottom) If the hypothesis is incorrect, then the high and low WM capacity groups should show a similar pattern regardless of motivation.

Experiment 2 Methods

20 new neurotypical right-handed University of Nevada students (mean age: 21.95, SD: 3.28, 12 females) participated. Participants were screened for use of neuroleptic, hypnotic, or seizure medications. Participants reported no history of neurological or psychiatric symptoms or head injuries. All procedures were conducted in accordance with the University of Nevada Institutional Review Board. Participants were compensated $15/hour in addition to what was earned in the Experiment and signed informed consent documents. No participants also took part in Experiment 1.

The WM task described in Experiment 1 will be used with two changes. First, the blocks varied by motivational load rather than strategy. Participants completed blocks of trials with low or high financial incentive. The low incentive block provided feedback after

each trial and participants received $.01 per correct trial. Participants received $.25 in the high incentive block. Second, participants received feedback after each trial informing them if they were correct or incorrect. Participants were not penalized for incorrect answers. At the end of the Experiment, participants were asked to report their level of motivation and what strategy they employed. Participants were not be financially penalized for incorrect trials. There was 2 counterbalanced stimulation conditions: anodal or sham. The left DLPFC will be stimulated (10 min, 1.5 mA).

Experiment 2 Analysis

For each participant, we calculated normalized difference scores for each session (anodal, sham) and strategy (active, passive) as follows: [(session accuracy – preliminary accuracy)/(session accuracy + preliminary accuracy)]. High and low WM capacity groups were determined by a medium split on the performance on the OSpan (high mean 19.9 (1.60), low mean 12.3 (4.89)).

Each block of trials lasted exactly 28 seconds followed by a 15 second rest period. The blocks were an additional 3 seconds longer than Experiment 1 due to feedback after each response. The fNIRS data was parsed to collect an average HBO level for the final 20 seconds of each block for each of the three channels. As above, we calculated normalized difference scores for each of the 3 detector channels, session (anodal, sham), and strategy (active, passive) as follows: [(session HBO level – preliminary HBO level)/(session HBO level + preliminary HBO level)].

Experiment 2 Results

Behavioral Effects

In Experiment 2, we were interested in understanding how participant motivation might play a role in the difference in performance between participants with different WM capacities. We hypothesized that providing financial motivation, the low WM capacity participants would increase performance along with establishing a beneficial effect of tDCS to match that of the high WM capacity participants. To investigate this hypothesis, we conducted a two session (anodal, sham) x two motivation condition (high, low) repeated-measures ANOVA with the between group factor of WM capacity (high, low) for the normalized difference scores. There were no significant main effects of tDCS session ($F_{1, 18} = 1.73$, $p = .21$, partial $\eta^2 = .09$), or motivation condition ($F_{1, 18} = 3.12$, $p = .09$, partial $\eta^2 = .15$). The interaction between tDCS condition and motivation reached significance ($F_{1, 18} = 4.81$, $p = .04$, partial $\eta^2 = .21$), such that participants had the greatest improvement from the preliminary task following anodal tDCS and when the motivation level was high (Figure 14, 15). These two factors when taken together (anodal tDCS + high motivation) lead to the greatest improvement for the high WM capacity group, however the three-way interaction of tDCS condition x motivation level x WM capacity group did not reach significance ($F_{1, 18} = .02$, $p = .89$, partial $\eta^2 < .01$). All other interactions failed to reach significance (all p's > .66). Participants reported no differences in motivation level between WM capacity groups.

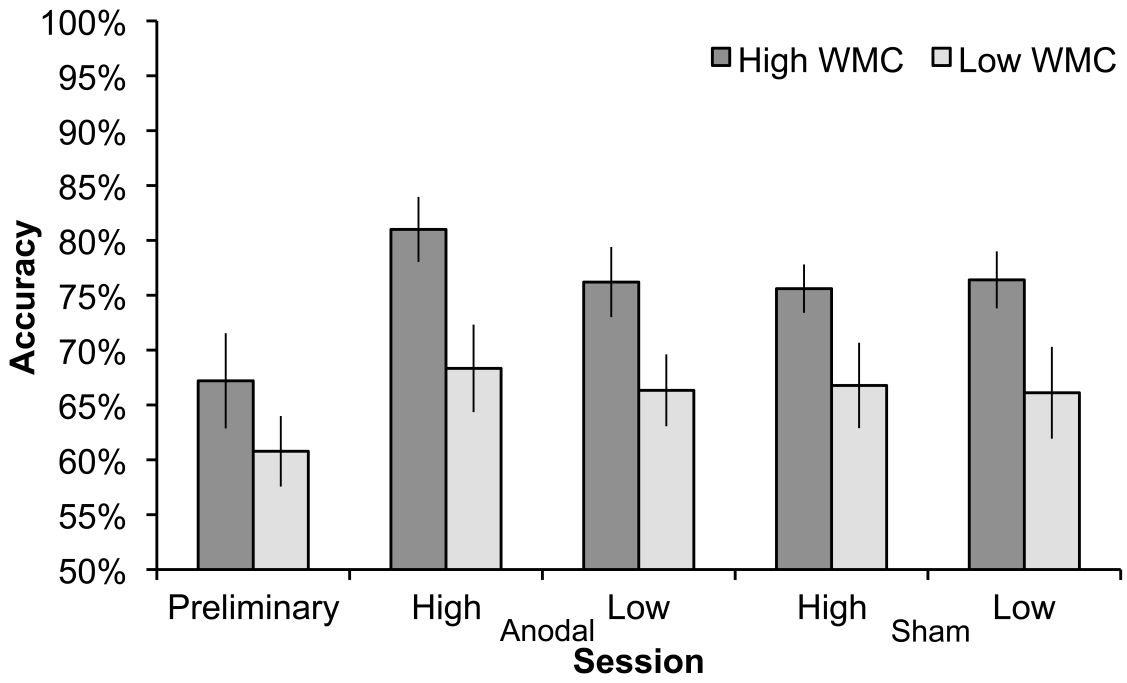

Figure 14: Accuracy on the WM recognition task in Experiment 2. The dark gray bars represent the high WM capacity group and the light gray bars represent the low WM capacity group. While not significant ($p = .16$) the high WM capacity participant s outperformed the low WM capacity participants on the preliminary trial. Both groups improved from the preliminary task across all tDCS and motivation conditions. The largest increase was for the high motivation condition during anodal tDCS for the high WM capacity group. The low WM capacity group's performance across all tDCS and motivation sessions matched that of the high WM capacity group's preliminary performance.

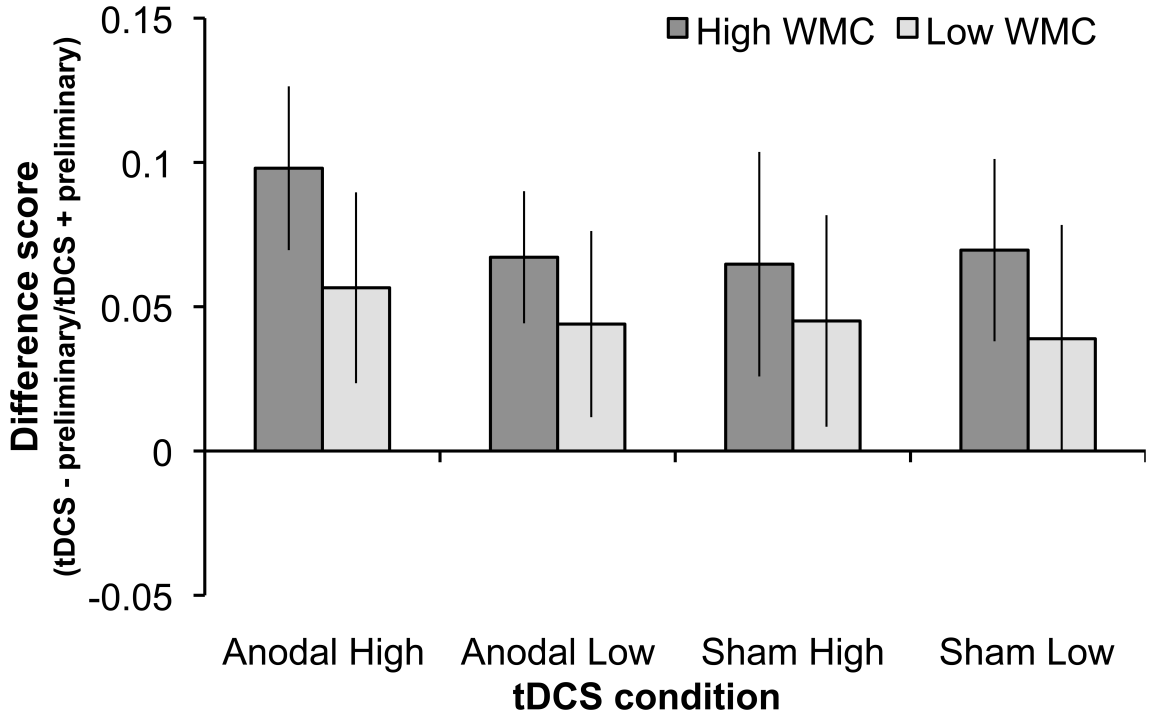

Figure 15: The normalized difference scores from preliminary task for each tDCS and motivation condition for high and low WM capacity groups' accuracy. Both WM capacity groups had similar increases in performance across all sessions. The high WM capacity group had the greatest increase in performance in the anodal tDCS and high motivation session, however this improvement was no significantly different from the low WM capacity group.

Functional Near-Infrared Spectroscopy Results

We were interested in how tDCS would alter the left DLPFC BOLD signal as measured by fNIRS. Furthermore, we were interested in understanding group differences in the fNIRS difference scores between tDCS and motivation conditions. To answer these questions, we conducted a two session (anodal, sham) x two motivation condition (high, low) x three detector channel repeated-measures ANOVA with the between group factor of WM capacity for the normalized difference scores. There was no significant main effect of tDCS ($F_{1, 18} = 3.37$, $p = .08$, partial $\eta^2 = .16$), motivation condition ($F_{1, 18} = 2.70$, $p = .11$, partial $\eta^2 = .13$), or fNIRS channel ($F_{2, 36} = 0.11$, $p = .90$,

partial η^2 = .01). The interaction of tDCS (anodal, sham) x motivation (high, low) x fNIRS channel x WM capacity (high, low) was significant ($F_{2, 36}$ = 3.66, p = .03, partial η^2 = .17), such that the low WM capacity group showed the greatest increase in blood flow as compared to the preliminary task across all channels in both motivation and tDCS conditions (Figure 16, 17). All other interactions were not significant (all p's > .20).

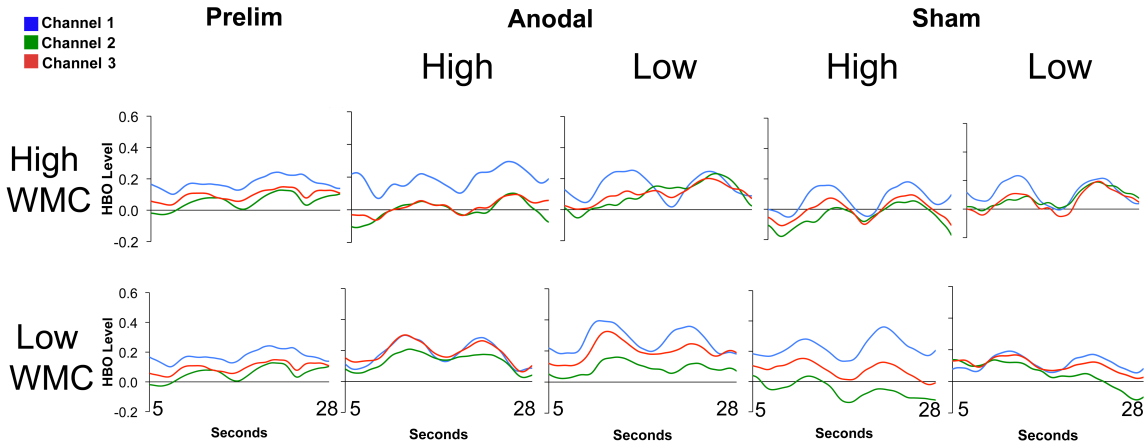

Figure 16: fNIRS data plotted as the HBO level through the block. The colors represent the three different channels. Graphs are plotted for the high WM capacity group (top row) and the low WM capacity group (bottom row). Plots represent data from the final 20 seconds of the trial averaged across all trials for that tDCS and strategy condition.

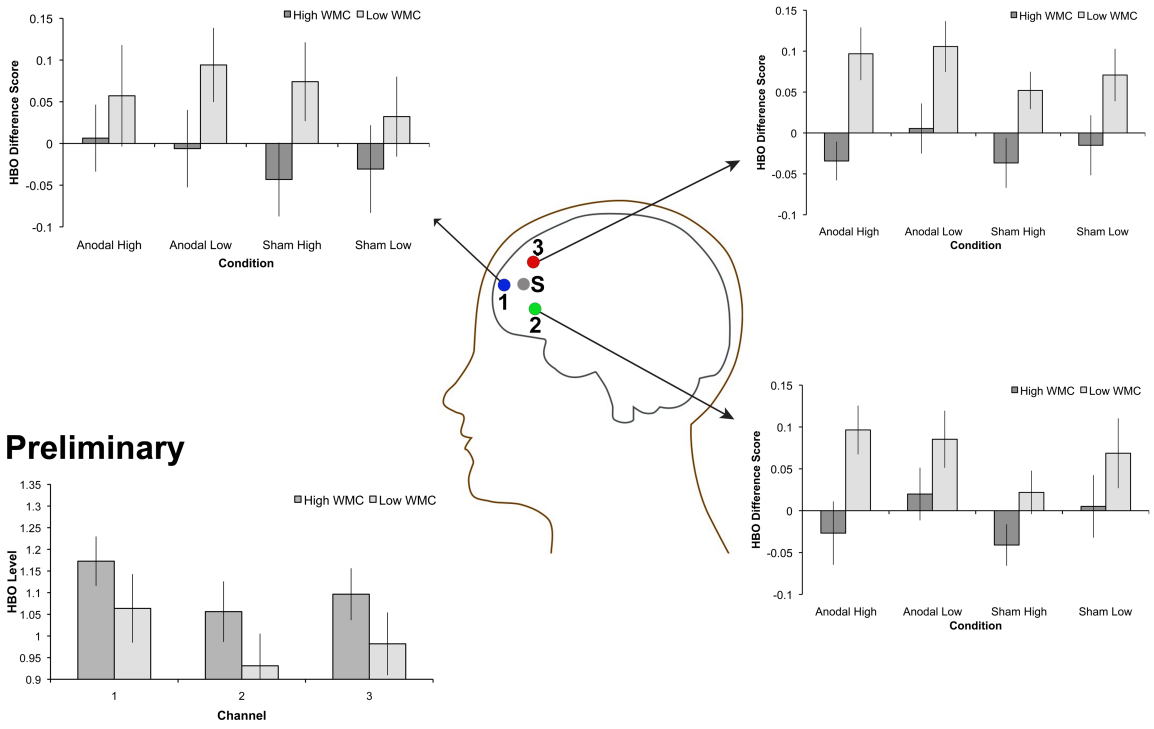

Figure 17: The difference scores for HBO levels between the preliminary task and each of the tDCS and motivation conditions for the high and low WM capacity groups at channel 1, 2, and 3. Across all channels, the high WM capacity group showed little to no change in HBO levels from preliminary across both tDCS and motivation conditions. The low WM capacity group showed in increase across both tDCS and motivation conditions at each of the three channels. Bottom Left) The raw HBO levels during the preliminary task. Both the high and low WM capacity group had similar levels of oxygenated blood during the preliminary task prior to both tDCS and motivation instructions.

Experiment 2 Discussion

In Experiment 2, we were interested in the effect financial motivation has on WM performance, particularly for the low WM capacity group. The first question was whether the high motivation condition would improve performance of the low WM capacity group to match that of the high WM capacity group. As seen in Figure 14 and 15, the low WM capacity participants improved equally across both tDCS and motivation conditions. Furthermore, the improvement was not significantly different from that of the high WM capacity participants. Anodal tDCS combined with high financial motivation had the greatest improvement for the high WM capacity participants, however this was not

significantly different from that of the low WM capacity participants. The improvement seen in the low WM capacity participants appears to be encouraging at first glance, the tDCS sessions all demonstrated equal performance to that of the high WM capacity preliminary session (Figure 14), however, this could be explained by practice effects as the preliminary task always came first. The task used in Experiment 2 was the same as Experiment 1 where there were no practice effects in the low WM capacity participants. The fact that the low WM capacity participants had equal improvement during the sham and low motivation condition as during the anodal and high motivation condition makes it difficult to believe that financial motivation alone is what is driving the improvement in behavioral performance.

Neurally, the data demonstrate that the low WM capacity group had a large increase in HBO levels from the preliminary task across all tDCS and motivation conditions (figure 17). This partially supports our prediction, as we believed that high motivation level should increase HBO levels at the left DLPFC for low WM participants. The high WM capacity participants had no change at all 3 channels across each tDCS and motivation condition. This could be explained by financial motivation having a small influence on motivation in the high WM capacity that already performed superior to the low WM capacity participants during the preliminary task. The low WM capacity participants had a large increase in HBO levels regardless of tDCS and motivation condition, which could represent increased effort at the presence of monetary reward.

The results of Experiment 1 found that anodal tDCS lead to increased blood flow for the high WM capacity participants, even in conditions (anodal tDCS, passive strategy), which should have lead to decreased performance. If anodal tDCS increases blood flow at the site of stimulation, then we should have seen an increase from the preliminary task during the anodal tDCS sessions for the high WM capacity participants

as seen in Experiment 1. This was not observed in Experiment 2, as the high WM capacity participants had little to no change in any condition as compared to the preliminary task.

Another recent study found that the right lateral orbitofrontal cortex (OFC) activates the left DLPFC differently during WM tasks that vary by motivation (Szatkowska et al., 2008). During the low motivation condition (no financial reward) on a verbal 2-back task, the right lateral OFC activates the left DLPFC, whereas in the high motivation condition the right lateral OFC has an inhibitory effect on the left DLPFC. This was an unexpected finding, and was explained by the researchers that the right lateral OFC is active during high stress conditions, such as during financial reward trials. They further state that the inhibitory effect of the right lateral OFC on the left DLPFC could reflect the stress-induced attenuation of executive functions. This is supported by findings demonstrating that the right lateral OFC is involved in the experience of psychological stress (Wang et al., 2005). Our findings are difficult to compare to these fMRI data, as tDCS likely had an effect on both the DLPFC and OFC due to the nature of the diffuse current flow and electrode size. Our fNIRS data represent the area of the brain directly surrounding the center of the tDCS anodal electrode. Channel 1 is the closest in proximity to the OFC, however with the infrared light only penetrating 1.3 cm in to the cortex it is unlikely to be detecting OFC activity. Future studies, which a large fNIRS array would properly measure HBO level changes in all PFC regions in both the left and right hemisphere. However in the current experimental design, increasing the fNIRS array was not feasible with the limited amount of set up time following tDCS application.

The results of Experiment 2 seek answer the question put forth in aim 2. We predicted that effective strategy use would allow for equivalent performance between low

and high WM capacity participants and tDCS benefits both groups. This turned to be the case behaviorally, as the low WM capacity participants performance on the tDCS sessions (active, sham) matched that of the high WM capacity performance's preliminary session. However, the low WM capacity participants improved equally across both tDCS and motivation conditions. Financial motivation may be one of the factors that can successfully lead to greater benefits from tDCS in those participants who show little benefit following stimulation. However, other non-monetary ways of increasing motivational drive should continue to be investigated for reliable tDCS effects to be seen across all individuals.

Chapter III

General Discussion

The present research explored the role of individual differences in cognitive studies that use tDCS to modulate performance in WM tasks. This may seem like a rather trivial and unimportant area to the general population, however the use of tDCS is rapidly expanding, as is the public knowledge and use of noninvasive neurostimulation techniques. With the increasing amount of clinical, cognitive, and recreational use of tDCS, understanding how neurostimulation will affect individuals is vital. The use of tDCS in home settings for recreational cosmetic neuroenhancement is on the rise. Numerous websites have instructions for building your own tDCS device or ordering one of their own products. These companies sell their product as a way to boost cognition and improve performance on activities in daily living. With the increasing use of this technique in settings that are not research or therapy oriented comes the risk that people are actually doing harm.

The goal of this dissertation was to investigate several factors that might predict both beneficial and negative effects of tDCS on WM. In two earlier experiments, we found that individuals responded differently to tDCS due to factors such as WM capacity and education. For certain factors (e.g. low WM) where previous tDCS studies showed null or negative findings, we investigated ways to reverse the effects via strategy use and extrinsic motivation. The present results offer some insight in to factors that predict tDCS benefit and how tDCS changes behavior in the cortex through the use of fNIRS.

Overview

The goal of Experiments 1 and 2 was to investigate how tDCS modulates cortical activity through the use of fNIRS. Furthermore, we attempted to remediate previous null findings in half of our participants through the use of explicit strategy instructions and by providing financial motivation. Using fNIRS to measure the HBO level in the left DLPFC, the site targeted by tDCS, we measured baseline HBO levels during the preliminary task for each group. We also used fNIRS to measure HBO levels during the same WM recognition task following tDCS and compared how blood flow changed. This gave measurements of HBO levels at baseline and following sham and anodal tDCS for each WM capacity group. We felt this was an important contribution to the tDCS literature as most studies only rely on subtle behavioral changes in performance rather then investigating what is occurring within the cortex.

We were first interested in investigating the influence of strategy on the WM benefit following tDCS. We predicted that poor strategy use was to blame for the previous null findings in low WM capacity participants in our previous study (Jones & Berryhill, 2012). We hypothesized that by providing an active rehearsal strategy to the low WM capacity participants would enhance tDCS linked WM benefits, as previous

studies have found that low WM capacity participants employ strategies that are less effective than high WM capacity participants (Schelble et al., 2012). The results of Experiment 1 replicated those of our previous study (Jones & Berryhill, 2012); tDCS facilitated a greater performance benefit in high WM capacity participants compared to the low WM capacity participants, regardless of strategy use.

Next we were interested in measuring cortical blood flow before and after tDCS through the use of fNIRS. We wanted to observe how tDCS changes oxygenated blood levels within the cortex following tDCS rather then only relying on subtle behavioral changes. We predicted that active rehearsal strategy use would increase the HBO levels in the low WM capacity participants. The fNIRS data followed a similar pattern as the behavioral data; high WM capacity participants had a greater increase in HBO levels following anodal tDCS, regardless of strategy condition. The HBR changes following tDCS and strategy conditions were smaller than that of the HBO level changes and did not vary greatly between WM capacities (Appendices figure 1).

In Experiment 2 we were interested in the effect participant motivation level has on tDCS linked WM benefits. We hypothesized that low WM capacity participants may show no WM benefit due to a lower desire to perform well. In previous experiments, participants received extra credit or cash payment regardless of performance. Here, we rewarded participants with extra payment for every correct answer with two levels of reward ($.01 and $.25 cents). We further hypothesized that during the high motivation trials ($.25), the low WM capacity participants would be more driven to perform well and thus show increased beneficial effects of tDCS on WM performance. Lastly, we hypothesized that the high WM capacity group would not show a large benefit of financial reward, as they would already be intrinsically motivated to perform well during the preliminary task. Results demonstrated that all participants improved following tDCS

regardless of motivation and stimulation type. There was a larger benefit for the high WM capacity participants in the high motivation condition following anodal tDCS, however this was not statistically significant.

As with Experiment 1, we investigated changes in HBO level throughout the Experiment with the hope of understanding how tDCS and motivation interact to modulate cortical blood flow. We predicted that high motivation should increase blood flow to the left DLPFC for the low WM capacity participants. The fNIRS data show the opposite pattern of Experiment 1. The high WM capacity participants had little to no change from the preliminary task following tDCS regardless of motivation condition, despite the behavioral improvements. However, the low WM capacity participants had a large increase in HBO levels following tDCS as compared to the preliminary task. These increases were across both tDCS and motivation conditions. The HBR changes following tDCS and motivation conditions were smaller than that of the HBO level changes and did not vary greatly between WM capacities (supplementary figure 2).

Implications

The central purpose of this dissertation was to investigate the influence of strategy and motivation on WM benefits following tDCS. We predicted that effective strategy use and financial motivation would increase WM benefits in the low WM capacity participants. Furthermore, we were interested in recording neural blood flow within the cortex through the use of fNIRS. Elucidating how tDCS influences cortical activity is vital to the expanding field of neurostimulation research. The results of our previous studies demonstrated that tDCS is not appropriate for everyone based on individual differences in education level and WM capacity (Berryhill & Jones, 2012; Jones & Berryhill, 2012). The goal of Experiments 1 and 2 was to find ways in which

tDCS can be successfully applied to those who previously have shown no effect, such as those with low WM capacity.

The results of Experiment 1 are not encouraging for the prospect of widespread noninvasive neurostimulation. We find that effective strategy use has no impact on low WM capacity participants, which was the opposite of we predicted. Other strategies may be more effective for low WM capacity participants, however the active strategy was particularly effective for the high WM capacity group, the opposite of our hypothesis. The vast majority of reported preliminary task strategies closely related to passive recognition or active verbal rehearsal. The high WM capacity participants continued to show an increase in both anodal tDCS conditions regardless of strategy. This was supported by the neural data demonstrating that the high WM capacity participants also had a greater increase in oxygenated blood flow in the left DLPFC after tDCS as well as during active rehearsal conditions.

One interesting finding was that during the anodal tDCS and passive strategy condition, the high WM capacity participants had an increase in HBO levels (at channel 1) where the low WM capacity participants had a decrease in HBO levels. All participants reported adhering to the given strategy conditions, and we predicted that passive strategy use would lead to a decrease in HBO levels in the left DLPFC. This is intuitive as an active rehearsal strategy should drive more blood to the DLPFC and a passive strategy should lead to a decrease in HBO levels. However this finding of increasing HBO levels following anodal tDCS in high WM capacity participants where low WM capacity participants have a decrease in HBO raises questions about the physiological differences in the brain. If high WM capacity participants have a different BOLD response pattern in the cortex following tDCS, then there would be very little that could be done to remediate null findings in low WM capacity participants.

The Experiment 2 results follow the pattern seen in Experiment 1 and our previously published studies for the high WM capacity participants (Berryhill & Jones, 2012; Jones & Berryhill, 2012). The high WM capacity participants showed improvement in all tDCS and motivation conditions. However, unlike the previous studies, here, this WM improvement was not statistically different from the improvement in the low WM capacity participants. Furthermore, following all tDCS sessions, the low WM capacity participants' performance matched that of the high WM capacity group. However practice effects cannot be eliminated as a cause. The task was the same in both Experiment 1 and 2, making the likelihood of practice effects only being observed in Experiment 2 unlikely. The global improvement for the low WM capacity participants across high and low motivation conditions likely reflects an increased level of motivation to perform well. The fact that there was no difference between high and low motivation conditions might be due to a uniform level of effort once a financial motivation was put in to place. There was no difference between tDCS conditions as performance improved from the preliminary task uniformly across each condition for the low WM capacity participants.

The effect of motivation on cortical activity in Experiment 2 was specific to only the low WM capacity group. Despite having a similar behavioral improvement as the high WM capacity participants, the low WM capacity participants required a greater increase in blood flow to match the improvement. The high WM capacity participants had no increase in HBO levels following both tDCS and motivation conditions. This is somewhat encouraging as it demonstrates that the HBO changes seen following tDCS are likely not dependent on physiological differences in participants as Experiment 1 suggested. It is important to note however, that during the preliminary task in Experiment

2, the low WM capacity participants did have lower HBO levels than the high WM capacity group, which was not the case in Experiment 1.

An intriguing experimental finding from the present research is the impact financial motivation has on low WM capacity participants. We expected to see a difference between high and low motivation conditions as well as anodal and sham tDCS. Instead we saw a uniform improvement that was supported by an increase in HBO levels in only the low WM capacity participants. An explanation for this may be that the high WM capacity participants had increased level of motivation and thus increased blood flow during the preliminary task. The low WM capacity participants likely were not trying as hard as the high WW capacity participants on the preliminary task, which also would explain why the large increase in blood flow was only seen in one group of participants. However, reported levels of motivation during the preliminary task did not differ between WM capacity groups. One explanation for this may be that a reported motivation level of 4 (out of 5) does not represent the same level of effort for low WM capacity participants as it does for high WM capacity participants.

The roles of DLPFC and OFC in WM and motivation may explain the differential effect between WM capacity groups in HBO level changes. There was no difference between tDCS conditions or motivation conditions in HBO levels, however the mere presence of financial reward may have been enough to increase effort and thus increase blood flow. As previously discussed, the OFC interacts with the left DLPFC to either activate (low motivation/stress) or inhibit (high motivation/stress) in various conditions (Szatkowska, Bogorodzki, Wolak, Marchewka, & Szeszkowski, 2008). Participants reported no difference in all sessions in reported motivation level in Experiments 1 and 2. The simple presence of financial reward for correct trials was enough to improve

performance in all participants equally; the low WM capacity participants however had a lower starting point due to the lower performance on the preliminary task.

The Mechanism of Neurostimulation Benefits

One open question is what exactly is the mechanism that is responsible for the differential WM benefits following tDCS between participants. The results of Experiment 1 lend support for the notion that innate physiological differences between participants determine the extent of WM benefit following tDCS. Physiological differences in genotype, dopamine levels, or other cortical differences may be the reason that high WM participants score well on the OSpan task as well as receive beneficial WM effects from tDCS. The increase in HBO levels during the anodal tDCS and passive strategy condition in Experiment 1 support this interpretation, as passive strategy use should lead to a decrease in HBO levels in the left DLPFC. Our prediction of effective strategy use had no beneficial effect for the low WM capacity participants. This is despite previous research demonstrating equal performance once low WM capacity participants were instructed to use effective strategies (Schelble et al., 2012). This finding predicts that despite strategy use, low WM capacity individuals have no hope of matching the WM improvements of high WM capacity individuals.

However, the results of Experiment 2 weaken the case for physiological differences being the important mechanism for differential effects of tDCS. If physiological differences between participants are the most important factor in tDCS benefits then Experiment 2 should have shown that the high WM capacity participants receive an increase in HBO levels following anodal tDCS paired with superior performance gains. Instead, low WM capacity participants demonstrated equal improvement to the high WM capacity participants. The low WM capacity group showed

equivalent gains following tDCS, although overall performance accuracy remained lower than the high WM capacity group. This finding lends support for the notion that low WM capacity participants are simply less motivated participants. If motivation is the important mechanism in predicting tDCS linked WM benefits, this gives hope for future general use of tDCS because motivation is readily manipulated. Furthermore, potential at-home use is likely be dominated by those who are intrinsically motivated to improve cognitive functions, rather than those who are seeking extra credit for participation in laboratory studies.

One other possibility is tDCS affects broad cortical regions. Our current modeling (Figure 2) predicts that the flow of tDCS not only affects the regions directly below the electrodes, but also orbitofrontal and ventral temporal regions as the current passes through the cortex. We previously discussed the possibility of OFC regions contributing to motivational aspects of Experiment 2. The activity in ventral temporal regions represents deeper current changes within the cortex. If anodal tDCS is affecting subcortical regions involved in WM and reward, such as the basal ganglia, then this may help explain some of the behavioral effects we find in our current and previous tDCS experiments. The basal ganglia is known to have strong modulatory interactions in the cortex due to dopamine (Foerde & Shohamy, 2011; Shohamy, Myers, Kalanithi, & Gluck, 2008), a neurotransmitter that also is implicated in the effectiveness of tDCS (Boggio et al., 2006; Nitsche & Paulus, 2000). Furthermore, fMRI research has demonstrated that the basal ganglia modulates connectivity between frontal regions as well as asserts control on attentional resources (van Schouwenburg, den Ouden, & Cools, 2010). These findings continue to add to the complex interactions that likely affect the way in which tDCS modulates WM.

Limitations

One clear limitation of the present experiments is the limited sampling of the cortex via fNIRS. The handmade head strap we assembled only allowed for a limited number of emitters and detectors. Furthermore, the effect of tDCS is only temporary and we had a finite amount of time to apply the fNIRS set up before tDCS effects dissipate. Previous research has implicated regions adjacent to the DLPFC such as the OFC in responding differently to motivation (Szatkowska et al., 2008). The fNIRS set up used in Experiment 1 and 2 only measured HBO level at the point of stimulation. Had no time constraints been in place due to tDCS, a larger fNIRS array could be used to measure activity across the PFC in both hemispheres as well as the parietal cortex. The PPC has been implicated in patient (Olson & Berryhill, 2009), fMRI (Todd et al., 2005; Todd & Marois, 2004), as well as tDCS (Berryhill et al., 2010; Tseng et al., 2012) studies as being important during WM tasks, especially those probed by recognition. Had more regions of cortex been monitored with fNIRS we may have seen substantial group differences in different parts of the cortex rather than only the site of stimulation.

One other limitation of the study was the difference in duration of the preliminary task and the post-tDCS task. The preliminary task lasted 5-6 minutes and the post-tDCS tasks (strategy and motivation) lasted 20-21 minutes. We averaged the fNIRS data across blocks, but the preliminary task had fewer blocks to average across (8 blocks in preliminary, 15 blocks for each strategy/motivation condition in the post-tDCS task). We chose a short preliminary task, because we thought that a 20-minute preliminary task would have lead to extensive subject fatigue.

Conclusion

The increasing use of tDCS in research and clinical settings makes the full understanding of exactly how it works a critical point of investigation. The use of tDCS in clinical settings has been shown to be a reliable, noninvasive, and relatively inexpensive tool for recovering cognitive skills lost following stroke and other brain injuries (Hamilton, Chrysikou, & Coslett, 2011), particularly in motor and language recovery. The use of tDCS in research settings to manipulate cognitive components such as memory and attention often report null findings (Jacobson et al., 2012). These null findings may be due to individual differences, as tDCS may only be effective for half of the participants. Furthering our understanding of the factors that predict beneficial effects of neurostimulation will prove crucial to ongoing and future studies of WM in healthy participants.

Here, we demonstrate in Experiment 1 and 2 that tDCS has a beneficial effect on WM, however only more educated participants (Experiment 1) or those with high WM capacity (Experiment 2). These findings are troubling for the reliable use of tDCS to improve cognitive skills. In Experiment 1 we replicate this findings and demonstrate that providing low WM capacity participants with an effective strategy does not enhance tDCS effects. In the brain we observed a pattern of increased oxygenated blood flow following tDCS, but only in the high WM capacity participants. Experiment 2 did not follow the same pattern as the first three experiments. The low WM capacity participants improved uniformly across both low and high motivation conditions as well as across both tDCS conditions, similar to the high WM capacity group. The fNIRS data in the brain did show a group difference - only the low WM capacity participants had increased blood flow.

Strategy use did not predict tDCS benefit, as effective strategy use had no effect on the low WM capacity participants. Motivation may facilitate tDCS benefit, however this benefit was also seen equally in the sham condition. Rewarding participants with financial motivation, however, is not feasible for all research studies. Other factors that increase motivation level need to be established as having a beneficial effect on low WM capacity participants. Understanding all influential factors is vital to successful application of tDCS in rehabilitation, research, and future recreational use of neurostimulation. The risk of cognitive impairment after tDCS is worrisome. In order to have success with tDCS interventions, future research should determine the ideal tDCS parameters for maximizing the beneficial effects.

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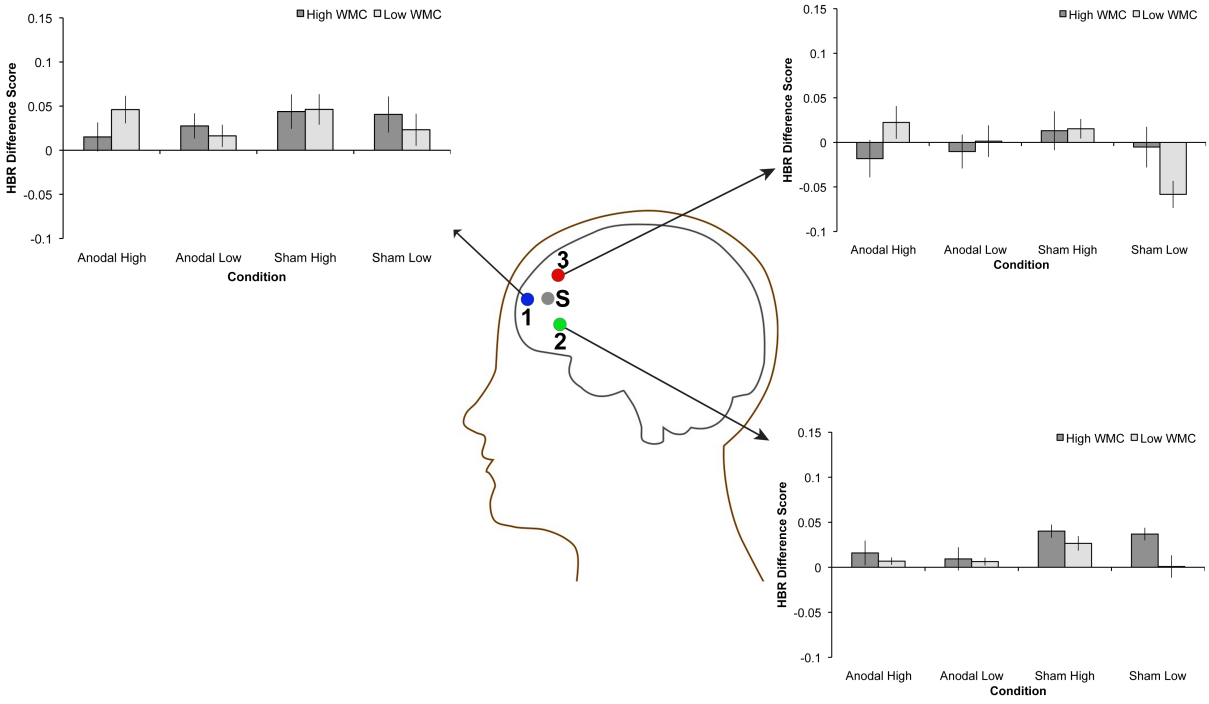
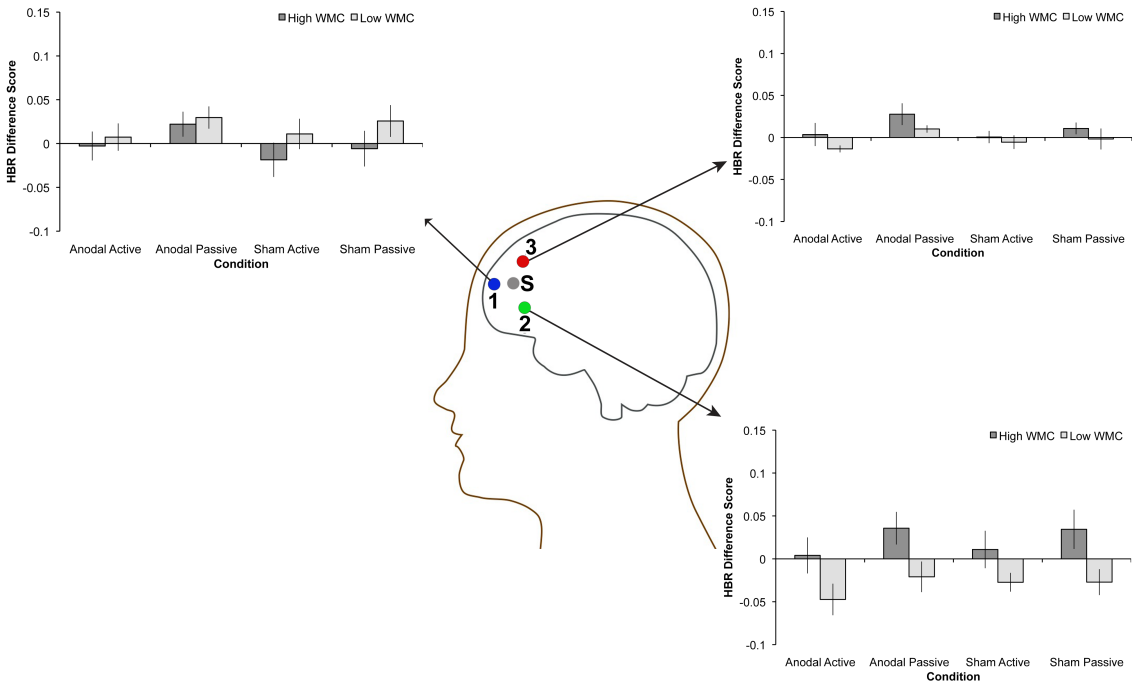
Appendices



Appendix Figure 1: Changes in deoxygenated blood as compared to the preliminary condition in Experiment 1. Bars represent differences scores of HBR level where values below the x-axis represent a decrease in HBR level from the preliminary task and values above the x-axis represent an increase in HBR levels from the preliminary task. The dark gray bars represent the high WM capacity group and the light gray bars represent the low WM capacity group. As compared to the HBO difference score graphs, changes in HBR level were similar between groups and smaller in magnitude.



Appendix Figure 2: Changes in deoxygenated blood as compared to the preliminary condition in Experiment 2. Bars represent differences scores of HBR level where values below the x-axis represent a decrease in HBR level from the preliminary task and values above the x-axis represent an increase in HBR levels from the preliminary task. The dark gray bars represent the high WM capacity group and the light gray bars represent the low WM capacity group. As compared to the HBO difference score graphs, changes in HBR level were similar between groups and smaller in magnitude.